TOXICOLOGICAL PROFILE FOR HYDROGEN SULFIDE

US. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for hydrogen sulfide was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

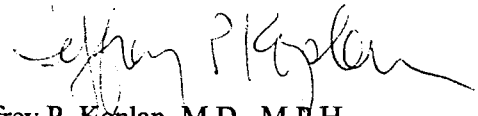
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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The toxicological profiles are developed in response to the Super-fund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Super-fund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,199O (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure,* by *type of health effect* death, systemic, immunologic, reproductive), and by *length of exposure* (acute. intermediate, and chronic). In addition, both human and animal studies are reported in this section"

> ***NOTE:*** Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

A TSDR Information Center
Phone: l-888-42-ATSDR or 404-639-6357 ***Fax: 404-639-6359***
E-mail: atsdric@cdc.gov ***Internet: http://www.atsdr.cdc.gov***

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History-The importance of taking an exposure histoi-y and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards: Skin Lesions and Environmental Exposures: Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume *II-Medical Management Guidelines for Acute Chemical Exposures-is* a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace .

Contact: NCEH, Mailstop F-29,4770 Buford Highway, NE, Atlanta, GA 30341-3724 l Phone: 770-488-7000 * FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 l Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19,4676 Columbia Parkway, Cincinnati, OH 45226-1998 l Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233,104 T.W. Alexander Drive, Research Triangle Park, NC 27709 l• Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #5 13, Washington, DC 20005 • Phone: 202-347-4976 •FAX: 202- 347-4950 •e-mail: ***aoec@dgs.dgsys.com*** • AOEC Clinic Director: http://occ-envmed. mc.duke.edu/oern/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. ***Contact:*** ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847- 228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for hydrogen sulfide. The panel consisted of the following members:

1. Alan Hall, M.D., FACEP, Clinical Assistant Professor, University of Colorado School of Medicine,Denver, CO

2. Edwin Kinkead, B.S., Private Consultant, Bonita Springs, FL

3. James Way, Ph.D., Professor, Texas A & M University, College Station, TX

These experts collectively have knowledge of hydrogen sulfide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(1)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about hydrogen sulfide and the effects of exposure. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Hydrogen sulfide has been found in at least 29 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which hydrogen sulfide is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to hydrogen sulfide, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS HYDROGEN SULFIDE?

Hydrogen sulfide is a colorless, flammable gas under normal conditions. It is commonly known as hydrosulfuric acid, stink damp, and sewer gas. Hydrogen sulfide smells like rotten eggs. People can smell hydrogen sulfide at concentrations as low as 0.5 parts of hydrogen sulfide per billion parts of air (ppb, 1 ppb is 1,000 times less than 1 part per million [ppm]). However, at concentrations over 100 ppm most people can no longer smell hydrogen sulfide, which makes it very

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dangerous. Hydrogen sulfide is found naturally and is also produced from man-made processes. It is found naturally in crude petroleum, natural gas, volcanic gases, and hot springs and is often the result of bacterial breakdown of organic matter. It is also produced from human and animal waste and can be found in sewage treatment facilities, sediments of fish aquaculture, and in livestock barns or manure areas. Industrial sources of hydrogen sulfide include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, and tanneries. Hydrogen sulfide is also produced by bacteria found in your mouth and gastrointestinal tract, and by enzymes in your brain and muscle. You will find more about hydrogen sulfide in Chapters 3 and 4.

1.2 WHAT HAPPENS TO HYDROGEN SULFIDE WHEN IT ENTERS THE ENVIRONMENT?

Hydrogen sulfide is released primarily as a gas and will spread in the air. However, in some instances, it may be released in the liquid waste of an industrial facility. When hydrogen sulfide is released as a gas, it may form sulfur dioxide and sulfuric acid in the atmosphere. Sulfur dioxide can be further broken down and is a major contributor to acid rain. Hydrogen sulfide is estimated to remain in the atmosphere for an average of 18 hours You will find more about what happens to hydrogen sulfide when it enters the environment in Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO HYDROGEN SULFIDE?

Your body makes small amounts of hydrogen sulfide. In the mouth, air levels between 1 and 100 parts of hydrogen sulfide per billion parts of air (ppb) have been found, while the average levels recorded in intestinal gas have been between 1 and 4 parts per million (ppm). The levels of hydrogen sulfide found in air and water are typically low. The amount of hydrogen sulfide in the air in the United States is between 0.11 and 0.33 ppb. In undeveloped areas of the United States, concentrations have been reported to be between 0.02 and 0.07 ppb. The amount of hydrogen sulfide found in surface water is low because hydrogen sulfide readily evaporates from water. Groundwater concentrations of hydrogen sulfide are generally less than 1 ppm; however measured sulfur concentrations in surface and waste waters have ranged from slightly less than 1 to 5 ppm.

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The general population may be exposed to quite high levels of hydrogen sulfide through misuse of drain cleaning materials and to lower levels from the accidental or deliberate release of emissions from pulp and paper mills, natural gas drilling and refining operations, and in areas with high geothermal activity, such as hot springs.

Persons who work in certain industries can be exposed to higher levels of hydrogen sulfide than the general population. These industries include the manufacture of rayon textiles, pulp and paper mills, petroleum and natural gas drilling operations, and waste-water treatment plants. Workers on farms with manure storage pits or landfills can also be exposed to higher levels of hydrogen sulfide than the general population. As a member of the general public you may be exposed to higher-than-normal levels of hydrogen sulfide if you live near a waste-water treatment plant, a gas and oil drilling operation, a farm with manure storage or livestock confinement facilities, or a landfill. Exposure from these sources is mainly from breathing air that contains hydrogen sulfide. You will find further information about hydrogen sulfide exposure in Chapter 5.

1.4 HOW CAN HYDROGEN SULFIDE ENTER AND LEAVE MY BODY?

Hydrogen sulfide enters your body primarily through the air you breathe. It can also be absorbed through the gastrointestinal tract and the skin. Once hydrogen sulfide enters your body several things can happen. Hydrogen sulfide may be broken down into more simple compounds, it may interact with proteins within your body, or it may leave unchanged. When hydrogen sulfide is broken down, it is partly excreted in the urine. Hydrogen sulfide that is not broken down is excreted through the lungs and feces. Additional information on how hydrogen sulfide can enter or leave your body is discussed in detail in Chapter 2.

1.5 HOW CAN HYDROGEN SULFIDE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

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One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Breathing hydrogen sulfide at concentrations greater than 500 ppm can be fatal within just a few breaths. Death is usually preceded by a loss of consciousness after one or more breaths, although a loss of consciousness does not necessarily mean that death will follow. Hydrogen sulfide is considered to be a “broad spectrum’ poison. This means that it can poison several different systems in the body. This variety of activity may be the reason that no single antidote, or treatment, has been found for hydrogen sulfide poisoning. Hydrogen sulfide can be especially dangerous because at concentrations over 100 ppm you might not be able to smell it, and therefore you would not realize that you were being overexposed. Deaths due to breathing in large amounts of hydrogen sulfide have been reported in a variety of different work settings, including sewers, animal processing plants, waste dumps, sludge plants, oil and gas well drilling sites, and tanks and cesspools. If you are exposed to lower concentrations of hydrogen sulfide, the symptoms that appear, such as eye irritation, a sore throat and cough, shortness of breath, and fluid in the lungs, will usually subside within a few weeks, but other changes such as memory problems may occur. Breathing in hydrogen sulfide on a long-term basis may result in fatigue, loss of appetite, headaches, irritability, poor memory, and dizziness.

Very little information is available on what happens when you drink or eat something with hydrogen sulfide in it, but there are no reports of humans poisoned by such exposures. Pigs that ate food containing hydrogen sulfide experienced diarrhea for a few days and lost weight after a period of about 105 days.

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Little information is available on what happens when you are exposed to hydrogen sulfide by getting it on your skin, although care must be taken with the liquefied product to avoid frost bite. It is known that hydrogen sulfide will irritate your eyes if you are exposed to the gas. These types of exposures are more common in certain occupational settings.

Hydrogen sulfide has not been shown to cause cancer in humans, and its possible ability to cause cancer in animals has not been studied thoroughly. Hydrogen sulfide has not been classified for its ability to cause or not cause cancer. There is some evidence that exposure to hydrogen sulfide may lead to an increase in spontaneous abortions in humans. However, the studies where this effect was reported are complicated by exposures to other chemicals and a lack of information on the amount of exposure to hydrogen sulfide.

1.6 HOW CAN HYDROGEN SULFIDE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children are likely to be exposed to hydrogen sulfide in the same manner as adults with the exception of adults at work. However, because hydrogen sulfide is heavier than air and because children are shorter than adults, children may be exposed to larger amounts of hydrogen sulfide than adults. Health effects in children that have been exposed to hydrogen sulfide have not been studied much. It is likely that exposed children will experience effects similar to exposed adults. It is not known whether children are more sensitive to hydrogen sulfide exposure than adults and is not known whether hydrogen sulfide causes birth defects in humans. For more information on the potential health effects of hydrogen sulfide on children see Sections 2.6 and 5.6.

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1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO HYDROGEN SULFIDE?

If your doctor finds that you have been exposed to significant amounts of hydrogen sulfide, ask whether children may also be exposed. When necessary your doctor may need to ask your State Department of Public Health to investigate.

Families can become exposed to excess hydrogen sulfide if they live near natural or industrial sources of hydrogen sulfide such as hot springs, manure holding tanks, or pulp and paper mills. Families may wish to keep visits to such places to a minimum.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HYDROGEN SULFIDE?

In the case of life-threatening hydrogen sulfide poisoning, measurements of blood sulfide or urinary thiosulfate levels may be used to confirm exposure. However, samples need to be taken within two hours of exposure in order to be useful. The tests for measuring sulfide in the blood or thiosulfate in the urine are described in Section 2.7.1.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an S-hour workday or a 24-hour day), the use of different animal studies. or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for hydrogen sulfide include the following:

EPA has established that hydrogen sulfide is a regulated toxic substance and is a hazardous substance as defined under the Federal Water Pollution Control Act. OSHA has established an acceptable ceiling concentration of 20 parts per million (ppm) for hydrogen sulfide in the workplace, with a maximum level of 50 ppm allowed for 10 minutes maximum duration if no other measurable exposure occurs. NIOSH has set a maximum Recommended Exposure Limit REL) ceiling value (10 minutes) of 10 ppm. A complete listing of federal and state regulations and recommendations are found in Chapter 7.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

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* Information line and technical assistance

Phone: l-800-447-1544
Fax: (404) 639-6359

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact:

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2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of hydrogen sulfide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in

determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for hydrogen sulfide. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques, Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or *are* acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in th interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2. HEALTH EFFECTS

2.2.1 Inhalation Exposure

2.2.1.1 Death

There have been numerous case reports of human deaths after acute exposure to presumably high concentrations (2500 ppm) of hydrogen sulfide gas (Beauchamp et al. 1984). NIOSH (1977a) reported that hydrogen sulfide was the primary occupational cause of unexpected death. Snyder et al. (1995), summarizing 10 years of data (1983-l 992) from the Poison Control Centers National Data Collection system, indicated that at least 29 deaths and 5,563 exposures were attributed to hydrogen sulfide during that time period. Most fatal cases associated with hydrogen sulfide exposure have occurred in relatively confined spaces, such as sewers (Adelson and Sunshine 1966), animal processing plants (Breysse 196l), waste dumps (Allyn 1931), sludge plants (NIOSH 1985a), tanks and cesspools (Campanya et al. 1989; Freireich 1946; Hagley and South 1983; Morse et al. 1981; Osbern and Crapo 1981), and other closed environments (Deng and Chang 1987; Parra et al. 1991). Almost all individuals described in these reports lost consciousness quickly after inhalation of hydrogen sulfide, sometimes after only one or two breaths (the so-called "slaughterhouse sledgehammer" effect). Many of the case studies involved accidental poisonings for which the concentrations and/or duration of exposure were not known (Allyn 1931; Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Freireich 1946; Hagley and South 1983; Morse et al. 1981). In some cases, the victims were exposed for a period of time ranging from a few minutes to an hour and were unable to be revived (Adelson and Sunshine 1966; Deng and Chang 1987; NIOSH 1991; Osbern and Crapo 1981).

Death occurring after acute exposure to hydrogen sulfide appears to be the result of respiratory failure or arrest, with most cases initially presenting with respiratory insufficiency, noncardiogenic pulmonary edema, coma, and cyanosis. Three men lost consciousness and died after entering a sewer containing high concentrations of hydrogen sulfide; all had the characteristic odor of hydrogen sulfide at autopsy and presented with cyanosis and pulmonary edema (Adelson and Sunshine 1966). After being exposed to hydrogen sulfide in a bathroom connected to a manure pit, a man developed nausea, vomiting, dizziness, and dyspnea, and died a few hours later; hemorrhagic bronchitis and asphyxiation were noted as the cause of death (Parra et al. 199 1).

Estimates of hydrogen sulfide exposure were available for some of the cases reported involving lethalities. After developing decerebrate responses to painful stimuli and partial seizures, with subsequent indications of brain stem damage, a 16-year-old boy died (Hagley and South 1983). He was exposed to what was presumed

to be hydrogen sulfide in a liquid manure tank; 2 weeks after exposure, hydrogen sulfide concentrations measured 30 cm below the tank manhole were >150 ppm, the detection limit of the equipment. In another incident, a 16-year-old boy was 10 meters away from an underground liquid manure storage tank, the contents of which had been agitating for 30-60 minutes; he began coughing, vomited, lost consciousness, and died (Morse et al. 198 1). Autopsy showed tracheobronchial aspiration of stomach contents, focal pulmonary hemorrhages and edema, and small petechial brain hemorrhages. Hydrogen sulfide concentrations were found to be >60 ppm (equipment detection limit) under similar conditions in the vicinity of the accident 2 days later. Although some other gases common to this environment were not detected, it is possible that there was simultaneous exposure to other compounds. A boy and his father were overcome and died after inhaling hydrogen sulfide gas from a discarded drum at a manufacturing dump (Allyn 193 1). Although the concentration of the gas inside the drum at the time of exposure was not known, a crude attempt was made to estimate exposure. Gas was collected from the drum 2 weeks after the accident and diluted 1:400 with air. A rat exposed to this dilution died after 40 seconds of exposure.

Three of five men, who lost consciousness within a few minutes of entering a partially drained underground liquid manure storage tank, died before reaching the hospital; autopsy showed that two had massive liquid manure pulmonary aspiration, while the third had fulminant pulmonary edema without manure aspiration (Osbem and Crapo 198 1). Markedly elevated heart-blood sulfide-ion levels indicated significant hydrogen sulfide exposure. Air samples analyzed about a week after the accident detected only 76 ppm of hydrogen sulfide, but the study authors noted that the environmental conditions were probably different (e.g., warmer weather, less-concentrated manure).

Two maintenance workers at an animal tanning company collapsed and died no more than 45 minutes after entering a sewer manhole; a hydrogen sulfide concentration of 200 ppm was obtained just inside the manhole 6 days after the accident (NIOSH 199 1). A worker at a poultry feather processing plant died after being exposed to hydrogen sulfide gas for an estimated 15-20 minutes (Breysse 1961). Testing performed later in the area where the exposure occurred indicated that hydrogen sulfide concentrations ranged from 2,000 to 4,000 ppm. Pulmonary, intracranial, and cerebral edema and cyanosis were noted at autopsy.

Claims for acute hydrogen sulfide exposure that occurred over a 5-year period (1969-l 973) in Alberta, Canada, primarily among petrochemical workers, were reviewed by Burnett et al. (1977). Acute effects noted included coma, disequilibrium, and respiratory insufficiency with pulmonary edema. Of 221 cases, there were 14 deaths. A follow-up study of 250 workers' claims for hydrogen sulfide exposure from 1979 to 1983

in Alberta, Canada, found 7 fatalities that usually involved the central nervous and respiratory systems; hepatic congestion and cardiac petechiae were also noted (Arnold et al. 1985). The difference in fatality rate (6% down to 2.8%) was attributed to improved first aid training and an increased awareness of the dangers of hydrogen sulfide.

Only very limited information is available on mortality in humans associated with chronic exposure to hydrogen sulfide. Bates et al. (1997), taking advantage of the fact that the New Zealand city of Rotorua is in a geothermally active area, conducted a retrospective ecological epidemiologic study in which they compared the mortality for selected diseases between residents in Rotorua and the rest of New Zealand. Rotorua uses geothermal energy for industrial and domestic heating purposes. Monitoring during the 1970s found levels of hydrogen sulfide as high as 1 mg/ m^3 (7 10 ppb); the most reliable data provided a median concentration of 20 $\mu g/m^3$ (14 ppb) with 35% of the measurements of 70 $\mu g/m^3$ (50 ppb), and 10% over 400 $\mu g/m^3$ (284 ppb). Mortality data examined were limited to the main organ systems known to be at risk in hydrogen sulfide exposure, i.e., the nervous, respiratory and cardiovascular/circulatory systems, and birth defects. Among these four mortality categories only deaths due to diseases of the respiratory system showed a significantly elevated standardized mortality ratio (SMR =1 .I 8; $p<0.001$). Because the population in the Rotorua area has markedly more Maori than in the rest of New Zealand, and because Maori disease and mortality rates are relatively high compared with those of the non-Maori population, further analysis was carried out with an adjustment for ethnicity. When these data were stratified by sex and ethnicity, female Maoris had an SMR of 1.61 ($p< 0.001$). Carrying the analysis to minor groupings of disease, significant increases in SMR were found for rheumatic fever and chronic rheumatic heart disease (SMR = 1.5;1 p=0.01), hypertensive disease (SMR= 1.61; $p < 0.001$), pneumonia and influenza (SMR = 1.20; p=0.008), and chronic obstructive respiratory disease and allied conditions (SMR = 1.20; p=0.004). In their analysis of the data, the authors note the numerous issues that can be raised with regard to ecologic studies such as theirs; the two principle issues being confounded by other exposures (e.g.V smoking) and by ethnicity misclassification. Despite the fact that the data indicate significant increases in SMRs, the study authors concluded that "no convincing evidence was found in this study of elevated rates of mortality in Rotorua compared with the rest of New Zealand." They caveat this conclusion with three considerations: not all causes of deaths were considered, exposures were inadequately characterized, and ethnicity misclassification could have obscured important causes of mortality.

Studies performed using laboratory animals exposed to high concentrations of hydrogen sulfide gas have yielded results similar to those observed in humans exposed at high levels. Exposure of Sprague-Dawley rats

to 1,655 ppm killed all 5 animals within 3 minutes (Lopez et al. 1989). All male Fischer-344 rats exposed to 500-700 ppm hydrogen sulfide gas for 4 hours died, while no rats died when exposed to concentrations up to 400 ppm under these conditions (Khan et al. 1990; Lopez et al. 1987, 1988a, 1988b). Ten of 10 male Wistar rats died after a 12-minute exposure (mean) to 800 ppm hydrogen sulfide (Beck et al. 1979). Concentrations of 335-587 ppm that cause death in 50% of the animals tested (LC_{50}) have been reported in Sprague-Dawley, Fischer-344, and Long Evans rats exposed to hydrogen sulfide gas for 2-6-hour periods (Prior et al. 1988; Tansy et al. 1981), although there were fewer deaths in approximately the same dose range in another study using Fischer-344 rats (Prior et al. 1990). No mortality was reported when male Wistar rats were exposed to up to 500 ppm hydrogen sulfide for 2 hours (Higuchi and Fukamachi 1977).

No deaths occurred among 30 adult female CB-20 mice exposed to 100 ppm hydrogen sulfide for 2 hours/day for 1 day (Elovaara et al. 1978), nor in 20 adult female NMRI mice exposed for l-4 days (Savolainen et al. 1980). All 6 mice exposed to 722 ppm hydrogen sulfide for 50 minutes died, while 1,872 ppm hydrogen sulfide killed a group of 6 mice in 10 minutes (Smith and Gosselin 1964). Five Japanese white rabbits died within 30 minutes of exposure to 500-l ,000 ppm hydrogen sulfide (Kage et al. 1992).

No mortality was noted during 90-day studies in which male and female Fischer-344 or Sprague-Dawley rats were exposed for 6 hours/day, 5 days/week, to up to 80 ppm hydrogen sulfide (CIIT 1983b, 1983c). Similar results were obtained at the same concentrations and conditions in a companion study using $B6C3F_1$ mice; although two high-dose animals were killed *in extremis,* and two control animals were found dead in the cage (CIIT 1983a).

All reliable LOAEL values for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration are recorded in Table 2-1 and plotted in Figure 2-1,

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	12 min				800 M (10/10 died)	Beck et al. 1979
2	Rat (Fischer- 344)	4 hr				500-700 M (4-6 used; all died)	Khan et al. 1990
3	Rat (Sprague-Dawley)	3 min				1655 M (5/5 died)	Lopez et al. 1989
4	Rat (Sprague-Dawley, Fischer-344, Long Evans)	2 hr				587 (LC_{50})	Prior et al. 1988
5	Rat (Sprague-Dawley, Fischer-344, Long Evans)	4 hr				501 (LC_{50})	Prior et al. 1988
6	Rat (Sprague-Dawley, Fischer-344, Long Evans)	6 hr				335 (LC_{50})	Prior et al. 1988
7	Rat (Fischer- 344)	4 hr				375 M (2/12 died)	Prior et al. 1990

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide- Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
8	Rat (Sprague-Dawley)	4 hr				444 (LC_{50})	Tansy et al. 1981
9	Mouse (CD-1)	50 min				722 F (6/6 died)	Smith and Gosselin 1964
10	Rabbit (Japanese white)	14-30 min				500-1000 (5/5 died)	Kage et al. 1992
	Systemic						
11	Human	>16 min	Resp	5 M			Bhambhani and Singh 1991
			Cardio	5 M			
			Metab	2 M	5 M (increased blood lactate during exercise)		
12	Human	30 min	Resp	5			Bhambhani et al. 1994
			Cardio	5			
13	Human	15 min	Resp	10			Bhambhani et al. 1996a
14	Human	2x 30 min	Musc/skel		5 M (decrease in citrate synthase when exercising at 50% maximum aerobic power)		Bhambhani et al. 1996b
15	Human	2x 30min	Cardio	10			Bhambhani et al. 1997
			Metab		10 (increase in blood lactate and decrease in oxygen uptake)		

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide- Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
16	Human	30 min	Resp		2[b] (bronchial obstruction in 2/10 asthmatics)		Jappinen et al. 1990
17	Rat (Fischer- 344)	4 hr	Resp		200 M (increase in protein and lactate dehydrogenase in lavage fluid; focal areas of perivascular edema; proteinaceous material in the alveoli)		Green et al. 1991
18	Rat (Wistar)	1 hr	Resp		100 M (increased respiration rate)		Higuchi and Fukamachi 1977
			Cardio		100 M (increased blood pressure, heart rate)		
19	Rat (Fischer- 344)	4 hr	Resp	10 M	50 M (15% reduction in lung cytochrome c oxidase activity)		Khan et al. 1990
20	Rat (Fischer- 344)	4 hr	Resp	50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991
21	Rat (Wistar)	20-60 min	Resp		75 M (slight congestion)		Kohno et al. 1991
			Cardio			75 M (cardiac arrhythmia; decreased heart rate)	
22	Rat (Fischer- 344)	4 hr	Resp		10 M (increased cellularity in nasal lavage fluid)		Lopez et al. 1987
23	Rat (Fischer- 344)	4 hr	Resp		83 M (mild perivascular edema)		Lopez et al. 1988a

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide- Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
24	Rat (Fischer- 344)	4 hr	Resp			400 M (severe inflammation and necrosis of respiratory and olfactory epithelium)	Lopez et al. 1988b
25	Rat (Fischer- 344)	4 hr	Ocular	200 M	400 M (epiphora)		Lopez et al. 1988b
26	Rat (Fischer- 344)	4 hr	Resp			375 M (moderate to massive pulmonary edema)	Prior et al. 1990
27	Gn Pig (NS)	11 d 1hr/d	Ocular		20 M (eye irritation)		Haider et al. 1980
28	Rabbit (mixed breeds)	1.5 hr or 5 d 0.5hr/d	Cardio			72 (changes in ventricular repolarization; cardiac arrhythmia)	Kosmider et al. 1967
Immunological/Lymphoreticular							
29	Rat (Fischer- 344)	4 hr		50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991
Neurological							
30	Human	30 min			2 (headache in 3/10 asthmatics)		Jappinen et al. 1990
31	Rat (Wistar)	20 min				800 M (unconsciousness)	Beck et al. 1979

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
32	Rat (Wistar)	2 hr		100 M	200 M (decreased response rate in discriminated avoidance task)		Higuchi and Fukamachi 1977
33	Rat (Fischer- 344)	4 hr		200 M	400 M (lethargy)		Lopez et al. 1988b
34	Gn Pig (NS)	11 d 1 hr/d			20 M (decreased cerebral hemisphere and brain stem total lipids and phospholipids)		Haider et al. 1980
35	Rabbit (mixed breeds)	1.5 hr				72 (unconsciousness)	Kosmider et al. 1967
INTERMEDIATE EXPOSURE							
Systemic							
36	Rat (Fischer- 344)	90 d 5d/wk 6hr/d	Resp	80			CIIT 1983b
			Cardio	80			
			Gastro	80			
			Hemato	80			
			Musc/skel	80			
			Hepatic	80			
			Renal	80			
			Endocr	80			
			Dermal	80			
			Ocular	80			
			Bd Wt	80			

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
37	Rat (Sprague-Dawley)	90 d 5d/wk 6hr/d	Resp	80			CIIT 1983c
			Cardio	80			
			Gastro	80			
			Hemato	80			
			Musc/skel	80			
			Hepatic	80			
			Renal	80			
			Endocr	80			
			Dermal	80			
			Ocular	80			
			Bd Wt	80 M 30.5 F	80 F (10% decrease in body weight)		
38	Rat (Sprague-Dawley)	gd1-ppd21 7hr/d	Metab		20 (50% increase in circulating glucose levels in dams)		Hayden et al. 1990a
39	Rat (Sprague-Dawley)	gd6-ppd21 7hr/d	Hepatic	50	75 (increased maternal liver cholesterol levels)		Hayden et al. 1990b
40	Rat (Sprague-Dawley)	gd6-20 6hr/d	Bd Wt	100 F	150 F (pregnant rats lost weight)		Saillenfait et al. 1989

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide- Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
41	Mouse (B6C3F1)	90 d 5d/wk 6hr/d	Resp	30.5 [c]	80 (inflammation of nasal mucosa)		CIIT 1983a
			Cardio	80			
			Gastro	80			
			Hemato	80			
			Musc/skel	80			
			Hepatic	80			
			Renal	80			
			Endocr	80			
			Dermal	80			
			Ocular	80			
			Bd Wt	30.5	80 (7-14% decrease in body weight)		
42	Pig (Crossbred)	17 d 24hr/d	Resp	8.5			Curtis et al. 1975
			Gastro	8.5			
			Hepatic	8.5			
			Renal	8.5			
			Ocular	8.5			
			Bd Wt	8.5			
	Immunological/Lymphoreticular						
43	Rat (Fischer- 344)	90 d 5d/wk 6hr/d		80			CIIT 1983b
44	Rat (Sprague-Dawley)	90 d 5d/wk 6hr/d		80			CIIT 1983c
45	Mouse (B6C3F1)	90 d 5d/wk 6hr/d		80			CIIT 1983a

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
Neurological							
46	Rat (Fischer- 344)	90 d 5d/wk 6hr/d		80			CIIT 1983b
47	Rat (Sprague-Dawley)	90 d 5d/wk 6hr/d		30.5 M 80 F	80 M (5% decrease in brain weight)		CIIT 1983c
48	Rat (Sprague-Dawley)	25 wk 5d/wk		50 M			Gagnaire et al. 1986
49	Mouse (B6C3F1)	90 d 5d/wk 6hr/d		80			CIIT 1983a
Reproductive							
50	Rat (Fischer- 344)	90 d 5d/wk 6hr/d		80			CIIT 1983b
51	Rat (Sprague-Dawley)	90 d 5d/wk 6hr/d		80			CIIT 1983c
52	Mouse (B6C3F1)	90 d 5d/wk 6hr/d		80			CIIT 1983a

TABLE 2-1. Levels of Significant Exposure to Hydrogen Sulfide- Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
Developmental								
53	Rat (Sprague-Dawley)	gd5-ppd21 7hr/d				20	(severe alterations in architecture and growth characteristics of Purkinje cell dendritic fields)	Hannah and Roth 1991
54	Rat (Sprague-Dawley)	gd5-ppd21 7hr/d		50		75	(decreases in brain amino acid levels of pups)	Hannah et al. 1989, 1990
55	Rat (Sprague-Dawley)	gd1-ppd21 7hr/d		75				Hayden et al. 1990a
56	Rat (Sprague-Dawley)	gd6-ppd21 7hr/d		75				Hayden et al. 1990b
57	Rat (Sprague-Dawley)	gd6-20 6hr/d		150				Saillenfait et al. 1989
58	Rat (Sprague-Dawley)	gd5-ppd21 7hr/d				20	(decreases in norepinephrine in the frontal cortex, increase in serotonin in the frontal cortex of pups)	Skrajny et al. 1992

[a]The numbers correspond to entries in Figure 2-1.

[b]Used to derive an acute-duration inhalation Minimal Risk Level (MRL) of 0.07 ppm for hydrogen sulfide by dividing by an uncertainty factor of 30 (10 for the use of a LOAEL and 3 human variability).

[c]Used to derive an intermediate-duration inhalation Minimal Risk Level (MRL) of 0.03 ppm for hydrogen sulfide by developing a human equivalent concentration NOAEL (NOAEL [HEC]) and dividing by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

B=both; Bd Wt=body weight; Cardio=cardiovascular; d=day(s); Endocr=endocrine; F=female; Gastro=gastrointestinal; gd=gestation day(s); Hemato=hematological; hr=hour(s); (LC50)=lethal concentration, 50% kill; LOAEL=lowest-observed-adverse-effect level; M=male; Metab=metabolism; min=minute(s); Musc/skel=musculoskeletal; NOAEL=no-observed-adverse-effect level; NS=not specified; ppd=post-partum day(s); Resp=respiratory; wk=week(s)

Figure 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation

Acute (≤14 days)

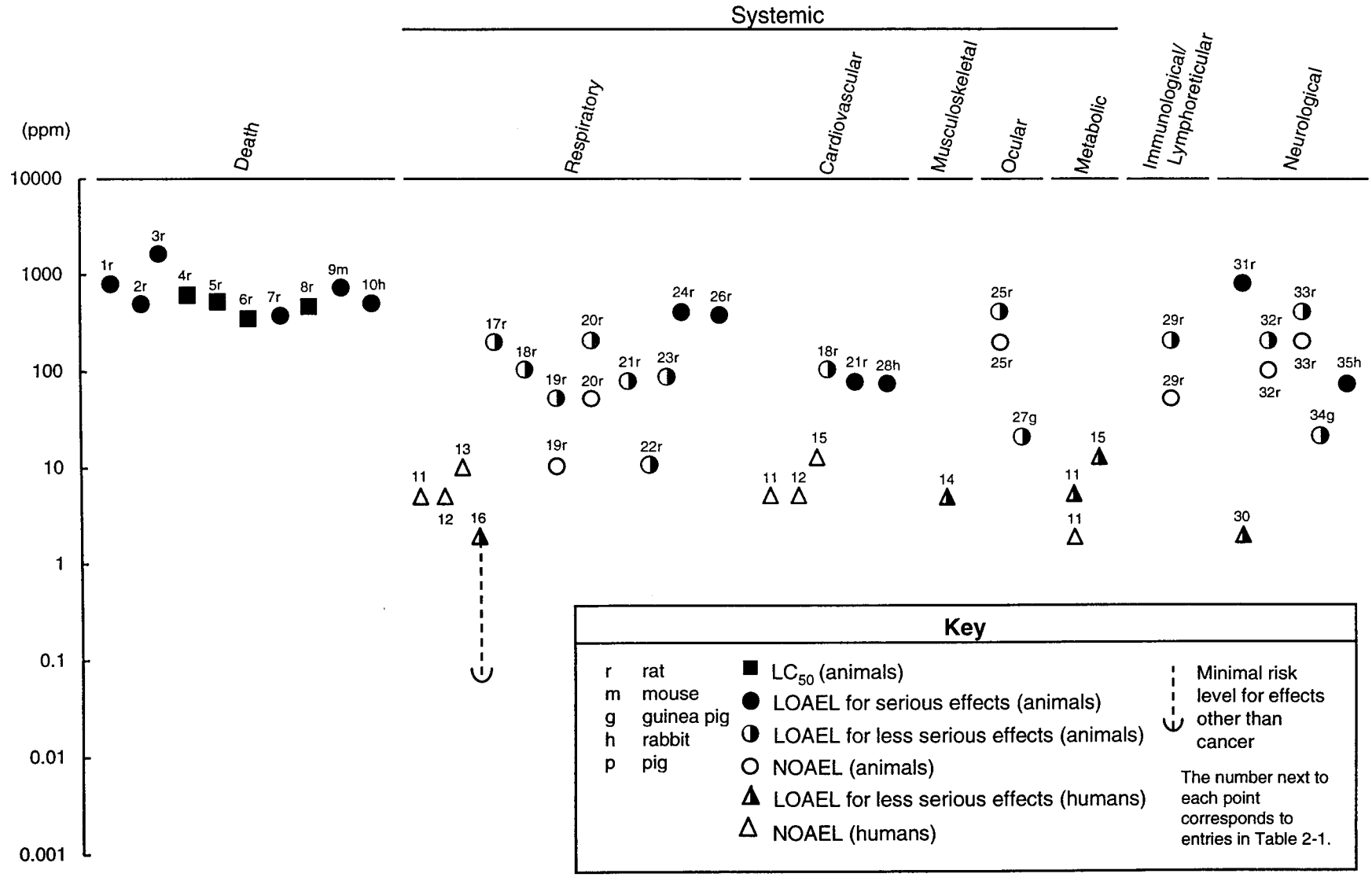


Figure 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(continued)*

Intermediate (15-364 days)

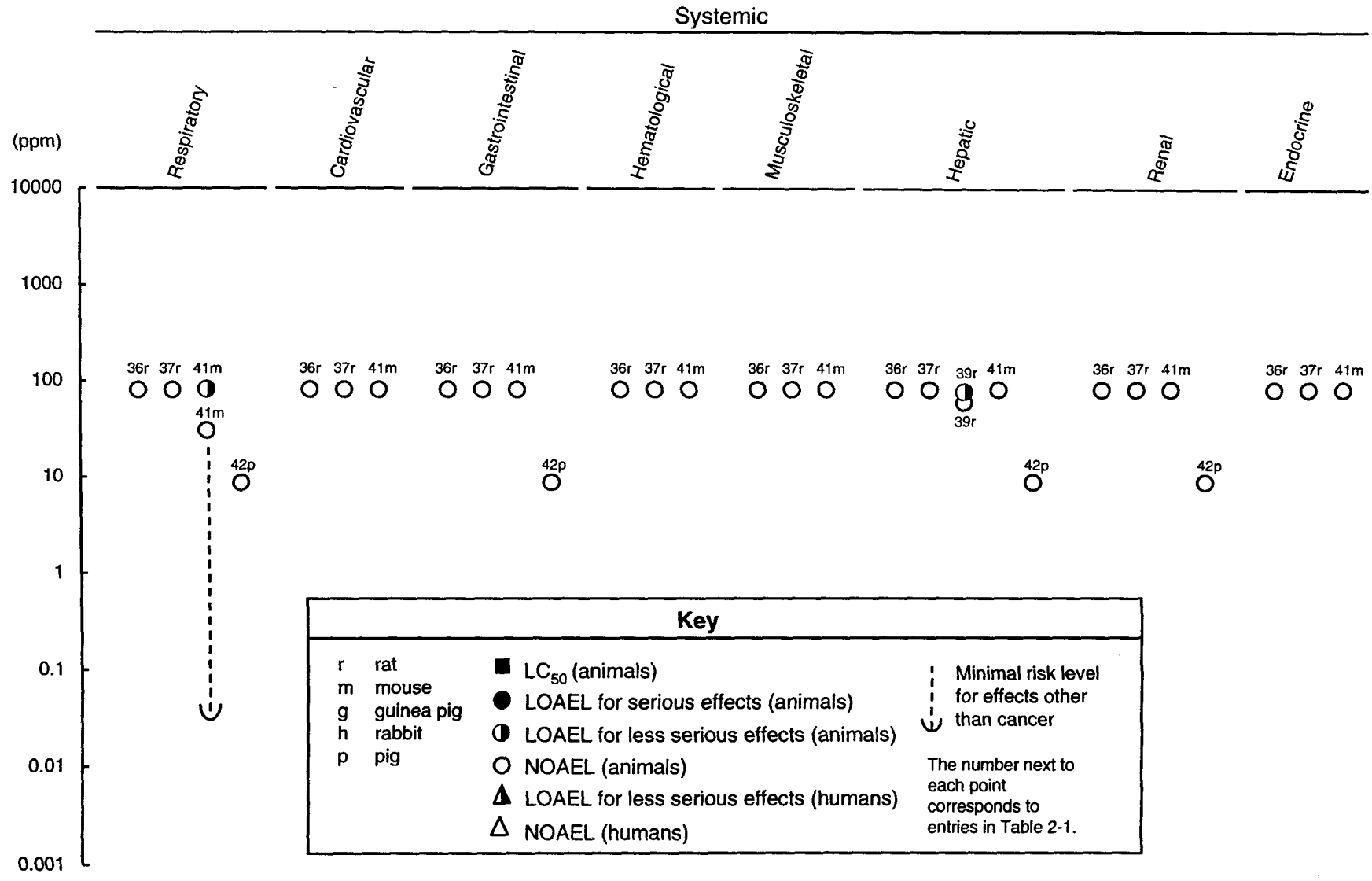
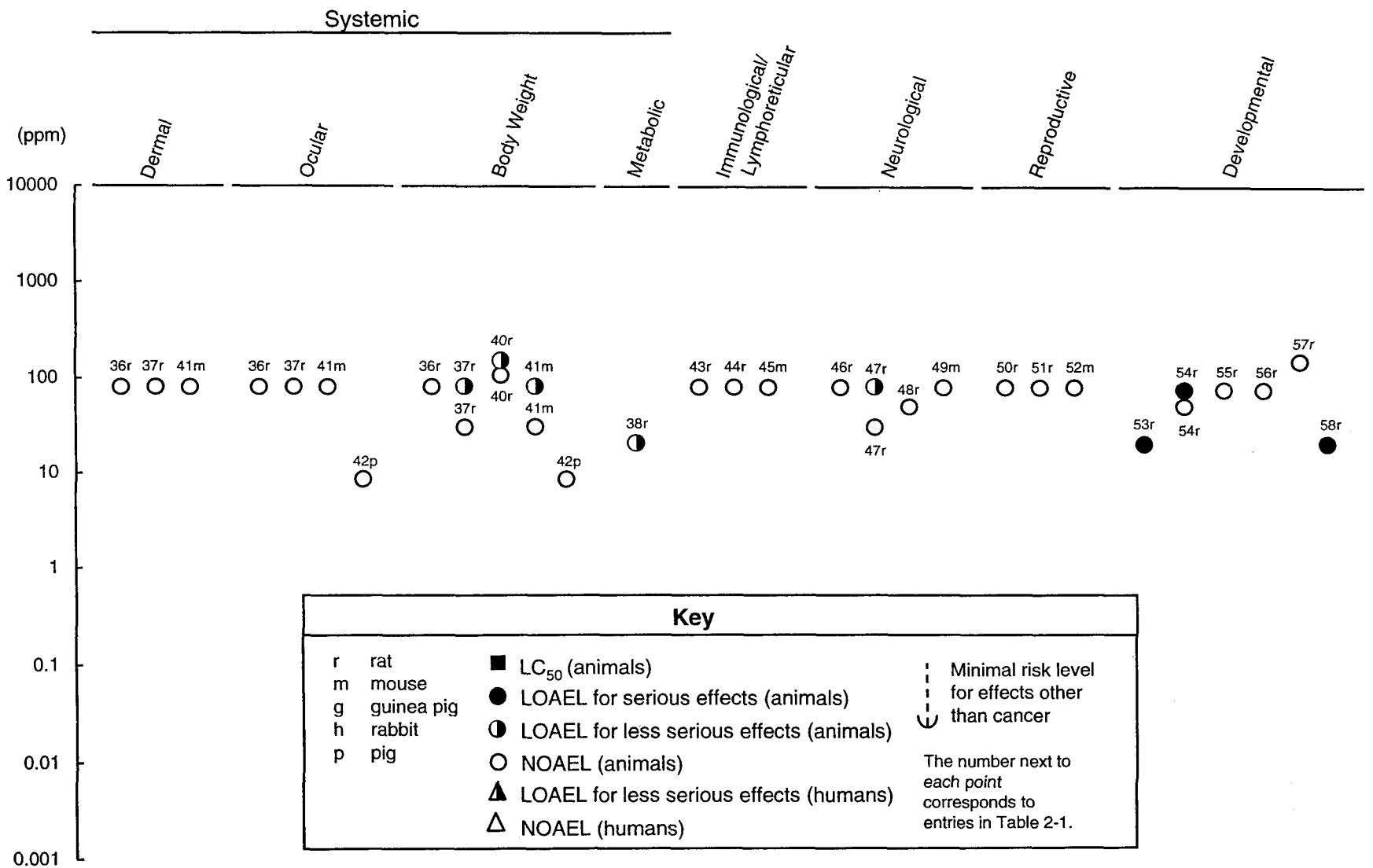


Figure 2-1. Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(continued)*

Intermediate (15-364 days)



2. HEALTH EFFECTS

Respiratory Effects. With acute accidental hydrogen sulfide exposure, numerous respiratory effects are observed. Death usually occurs after respiratory distress or arrest from the action of hydrogen sulfide on the hypothalamic respiratory center. Respiratory distress has also been noted in individuals who survived after acute exposures (Osbem and Crapo 1981; Peters 1981; Spolyar 1951). Other respiratory effects of acute hydrogen sulfide exposure include noncardiogenic pulmonary edema (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Thoman 1969; Tvedt et al. 1991a, 1991b), sore throat, cough (Burnett et al. 1977; Jaakkola et al. 1990), and dyspnea (Arnold et al. 1985; Burnett et al. 1977; Krekel 1964; Osbern and Crapo 1981; Parra et al. 1991; Ravizza et al. 1982; Stine et al. 1976; Thoman 1969). Cyanosis has been reported in a number of case reports and is believed to result from respiratory distress (Arnold et al. 1985; Tvedt et al. 1991 a, 1991 b). In most studies, exposure concentrations and/or durations were unknown. Among hydrogen sulfide exposure survivors, respiratory symptoms generally subsided within several weeks of exposure but occasionally persisted for several months or longer (Parra et al. 1991). Acute exposure to ~500 ppm hydrogen sulfide is considered to cause rapid respiratory failure (Beauchamp et al. 1984).

Respiratory distress was noted in 2 workers exposed to >40 ppm hydrogen sulfide for <25 minutes (Spolyar 1951). Male volunteers were exposed to hydrogen sulfide concentrations up to 5 ppm for more than 16 minutes after graded exercise that was performed to exhaustion (Bhambhani and Singh 1991). No effects on expired ventilation or maximum power output were noted, but exposure to 5 ppm resulted in a significant increase in maximum oxygen uptake compared to controls. At exposures to 2 and 5 ppm, the respiratory exchange ratio (RER) was decreased significantly compared to controls. The study authors attributed this to a nonsignificant trend toward increased oxygen uptake and decreased carbon dioxide output compared to controls (Bhambhani and Singh 1991). Another study examined the effects of inhalation of 5 ppm hydrogen sulfide on respiratory physiological parameters and found no changes in partial pressure of oxygen, partial pressure of carbon dioxide, oxygen uptake (VO_2), percentage of oxygen uptake (VO_2%), uptake of carbon dioxide (VCO_2) and V_E, or respiratory exchange ratio in male or female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). A third study found that inhalation of 10 ppm of hydrogen sulfide for 15 minutes at elevated metabolic and ventilation rates did not result in significantly altered pulmonary function test results in men and women (Bhambhani et al. 1996a).

Pulmonary function tests were performed on persons with asthma exposed to 2 ppm of hydrogen sulfide for 30 minutes (Jappinen et al. 1990). Although no significant changes were noted in airway resistance (Raw) or specific airway conductance (SGaw) as a group, 2 of 10 subjects showed changes in excess of 30% in both

Raw and SGaw, an indication of bronchial obstruction (Jappinen et al. 1990). No statistically significant changes were noted in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV,), and forced expiratory flow (Jappinen et al. 1990). Pulmonary function was unaffected following the same exposure protocol in 26 male pulp mill workers who had previously had daily hydrogen sulfide exposures, usually to <10 ppm (Jappinen et al. 1990). No significant changes were noted in FVC, FEV,, or bronchial responsiveness to histamine challenge in this group of workers, which included subgroups of smokers, workers with previous allergies, and atrophic individuals. Findings in this study are similar to those observed in Bhambhani et al. (1996a). Based on a LOAEL of 2 ppm for respiratory effects - bronchial obstruction (30% change in airway resistance) in 2/10 persons with asthma in the Jappinen et al. 1990 study, an acute inhalation MRL of 0.07 ppm was derived. An uncertainty factor of 30 was applied to the LOAEL, 10 for the use of a LOAEL, and 3 for human variability. Since persons with severe asthma were excluded from the study, an uncertainty factor of 3 is needed to protect all sensitive individuals including children.

Hessel et al. (1997) examined the pulmonary health effects of hydrogen sulfide exposure in a group of Canadian oil and gas workers. Exposure to hydrogen sulfide was assessed by questionnaire as was the occurrence of respiratory symptoms; in addition, smoking and occupational histories were conducted. Lung health was assessed via spirometric testing and by skin prick testing for six common antigens, The workers were divided into three exposure groups: none, gas exposure (sufficient to produce symptoms), and knockdown (exposure sufficient to cause unconsciousness). None of the lung function indicators (FEV_1 FVC, or FEV_1/FVC) differed significantly among the three groups. Significantly increased odds ratios (ORs) were seen only in those in the knockdown group who showed significant excesses for several symptoms, including: shortness of breath (OR = 3.55; 95% confidence interval (CI) = 1.02-12.4); wheeze with chest tightness (OR = 5.15; 95% CI 1.29-20.6); and attacks of wheeze (OR = 5.08; 95% CI = 1.28-20.6).

In a cross-sectional study of sewer and water treatment workers, Richardson (1995) evaluated the association of hydrogen sulfide exposures to reduced lung function using spirometric testing. Job titles were used to categorize sewer workers into high, medium, and low exposure groups; however, there was no quantification of hydrogen sulfide levels. Water treatment workers who are not occupationally exposed to hydrogen sulfide, were chosen as a comparison group. Findings included significant differences between spirometric values (FEV_1/FVC) of sewer and water treatment workers across a number of age strata, irrespective of smoking status**,** although smoking status reduced the impact somewhat. When stratified by presumed exposure to hydrogen sulfide, only those sewer workers with presumed high exposure showed a significant difference from water workers, although a dose-related trend in lung function at both medium and high exposures was

observed. In addition, the prevalence odds ratio for obstructive lung disease was 21 .0 (95% CI = 2.4-237.8) in nonsmoking sewer workers with presumed high hydrogen sulfide exposure when compared to nonsmoking water treatment workers. The prevalence odds ratio for sewer workers who smoke versus water treatment workers who smoke was 1.7 (95% CI = 0.2-13.6).

In a report comparing community responses to low-level exposure to a mixture of air pollutants from pulp mills, Jaakkola et al. (1990) reported significant differences in respiratory symptoms between polluted and unpolluted communities. The pollutant mixture associated with the pulp mills included particulates, sulfur dioxide, and a series of 'malodorous sulfur compounds.' Major contributors in the latter mixture include hydrogen sulfide, methyl mercaptan, and methyl sulfides. In this study the responses of populations from three communities were compared, a nonpolluted community, a moderately polluted community, and a severely polluted community. Initial exposure estimates were derived from dispersion modeling; these estimates were subsequently confirmed with measurements taken from monitoring stations located in the two polluted communities. These measurements indicated that both the mean and the maximum 4-hour concentrations of hydrogen sulfide were higher in the more severely polluted community (4 and 56 $\mu g/m^3$; 2.9 and 40 ppb) than in the moderately polluted one (2 and 22 $\mu g/m^{3;}$ 1.4 and 16 ppb). Particulate measurements made concurrently, and sulfur dioxide measurements made subsequently, showed a similar difference in the concentrations of these two pollutants between the two polluted communities.

A cross-sectional, self-administered questionnaire was used to gather data on the occurrence (i.e., often or constantly) of a variety of symptoms and effects during 2 time periods (the past 4 weeks and the previous 12 months). Respiratory endpoints evaluated included cough, nasal symptoms, breathlessness or wheezing, numbers of respiratory infections, history of asthma, and chronic respiratory diseases. The occurrence of nasal symptoms and cough was found to be significantly greater in the subjects living in the two polluted communities when compared to those in the nonpolluted community. Breathlessness or wheezing was also increased although not to the level of significance. All three of these endpoints showed a dose-related increase; that is, the greatest occurrence of symptoms occurred in the more highly-polluted community, followed by the less polluted, and then the nonpolluted communities. Because of the mixed exposures, however, the role of hydrogen sulfide in these effects is unclear.

A subsequent report by Marttila et al. (1994b) examined the impact of long-term exposure to the same mixture of malodorous sulfur compounds on children from these same three communities. The findings in children, i.e., nasal symptoms and cough, in the most severely polluted community were similar to those

reported above and showed increased risks both for the 4-week and the 12-month intervals, although none of these risks reached statistical significance.

Marttila et al. (1995) also examined the relationship between daily exposure to malodorous sulfur compounds (measured as total reduced sulfur [TRS]) from pulp production and experience of symptoms in a small population living in the vicinity of a pulp mill. The major components of the malodorous sulfur compounds are hydrogen sulfide, methyl mercaptan, and methyl sulfides. This work was initiated due to the observation that an unusually high short-term exposure to malodorous sulfur compounds (maximum 4-hour concentrations of hydrogen sulfide at 135 $\mu g/m^3$ [96 ppb]) led to a considerable increase in the occurrence of ocular, respiratory, and neuropsychological symptoms (Haahtela et al. 1992). During the study period, daily mean TRS concentrations varied from 0 to 82 $\mu g/m^3$, and monthly mean concentrations varied from 3 to 19 $\mu g/m^3$. Following a baseline questionnaire, the study was conducted with 6 consecutive questionnaires after 3 predefined levels of exposure to TRS (daily mean <10 $\mu g/m^3$, medium exposure 10-30 $\mu g/m^3$, high exposure >30 $\mu g/m^3$). The study found a dose-related increase in the probability of both nasal (i.e., stuffy or runny nose) and pharyngeal irritation. For nasal symptoms the probability ratios were 3.13 (95% CI 1.25 to 7.25) and 8.50 (95% CI 3.19 to 18.64) for medium and high exposure, respectively. For pharyngeal symptoms, the probability ratios were 2.0 (95% CI 0.92-4.14) and 5.20 (95% CI 1.95 -1.99) for the medium and high exposure levels, respectively.

Partti-Pellinen et al. (1996) used a cross-sectional, self-administered questionnaire to assess the eye, respiratory tract, and central nervous system symptoms experienced by adults in a slightly polluted and a reference community. In the polluted community the mean annual TRS concentrations were 2-3 $\mu g/m^3$, the 24-hour average concentrations varied between 0-56 $\mu g/m^3$, and the maximum l-hour concentration was 155 $\mu g/m^3$; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 $\mu g/m^3$, the 24-hour average concentrations varied between 0-24 $\mu g/m^3$, and the maximum 1 -hour concentration was 152 $\mu g/m^3$; in the reference community the mean sulfur dioxide level was 1 $\mu g/m^3$, and the maximum l-hour concentration was 30 $\mu g/m^3$.

Symptoms evaluated over the previous 4 weeks and previous 12 months included eye irritation, nasal irritation, cough, breathlessness or wheezing, and headache or migraine. After adjusting for age, sex, smoking, history of allergic diseases, education and marital status, increased odds ratios were seen for all of theses symptoms at both time periods. However, significant increases in odds ratios were seen only for headache or migraine in the previous 4 weeks (OR = 1.82; 95% CT =1.06-31.5) and in the past 12 months (OR = 1.70;

95% CI = 1.05-2.73) and cough in the past 12 months (OR =1.64; 95% CI = 1 .01-2.64). These findings led the authors to conclude that the adverse health effects of TRS occur at lower concentrations than previously reported. However, these findings are also confounded by daily average levels of TRS as high as 56 μg/m^3 and by the presence of sulfur dioxide which, though occurring at the same mean annual concentration in the two communities, showed much higher peaks in the polluted community. Furthermore, no information was provided on particulate levels, which could also be important to these findings.

This series of studies (Jaakkola et al. 1990; Haahtela et al. 1992; Martilla et al. 1994a, 1994b; Marttila et al. 1995; Partti-Pellinen et al. 1996) report the results of the South Karelia Air Pollution Study which began in 1986 to evaluate the effects of air pollution on human health and the environment. In the early studies of this series, (Jaakkola et al. 1990; Haahtela et al. 1992; Marttila et al. 1994b), levels of hydrogen sulfide, sulfur dioxide, particulates, and methyl mercaptan were individually reported. In the later studies (Marttila et al. 1994a, 1995; Partti-Pellinen et al. 1996), a complex mixture of 'malodorous sulfur components' (that included hydrogen sulfide, methyl mercaptan, and methyl sulfides) was monitored as total reduced sulfur (TRS) using a method that first removes any sulfur dioxide, then oxidizes the TRS compounds to sulfur dioxide, and reports the results as μg/m^3 TRS. It is not possible, from the information provided, to determine precisely what proportion of the TRS is actually hydrogen sulfide, although the authors indicate that it is about two-thirds (Marttila et al 1994b). The fact that in virtually all of these studies, effects were linked to exposures to mixtures, even though hydrogen sulfide appears to have been the dominant sulfur compound, complicates interpretation of these results. It is probably reasonable to conclude that these studies demonstrate that low levels of hydrogen sulfide in combination with other sulfur-containing pollutants, and possibly due to combination with particulates and/or sulfur dioxide, can have an adverse effect on respiratory health. However, it is not possible at this time to determine whether it is the low annual average values of l-2 μg/m^3TRS, or the daily average concentrations (56 μg/m^3TRS) which are associated with these findings.

As discussed in more detail in Section 2.2.1.1, Bates et al. (1997) found a significant increase in mortality from diseases of the respiratory system for residents of the Rotorua area of New Zealand for the period of 198l-l990. Rotorua is in an area of high geothermal activity; sampling from a campaign in 1978 indicated a median concentration for hydrogen sulfide of about 20 μg/m^3 with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3. Problems with the analysis, however, led these authors to conclude that there were no clear indications of excess mortality.

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In addition to an increase in respiration rate that was noted in Wistar rats exposed to 100-200 ppm hydrogen sulfide for 1 hour (Higachi and Fukamachi 1977), a number of histological and biochemical changes have been noted in the respiratory tissues and fluids of animals acutely exposed to hydrogen sulfide. Cytotoxicity to both nasal or bronchioalveolar lavage and pulmonary cells was demonstrated in a study of male Fischer-344 rats exposed to 0, 10,200, or 400 ppm hydrogen sulfide for 4 hours and examined at 1,20, or 44 hours postexposure (Lopez et al. 1987). Cellularity of nasal lavage fluid was increased at all exposure concentrations, because of either exfoliation of degenerated epithelial cells at 1 hour, or exudation of polymorphonuclear leukocytes (PMNs) at 20 hours postexposure, which served as an indicator of cell damage. Altered pulmonary vascular permeability was indicated by increased protein in nasal lavage fluids in animals exposed to airborne concentrations of 400 ppm, but this condition resolved by 20 hours postexposure. Increased lactate dehydrogenase activity (at exposure levels of 200 and 400 ppm) and alkaline phosphatase activity (with exposure to 400 ppm) in bronchoalveolar lavage fluid observed in this study were indicative of toxic effects on the pulmonary epithelium. In addition, pulmonary alveolar macrophages from animals exposed by inhalation to airborne concentrations of 200 or 400 ppm hydrogen sulfide had some increase in cytoplasmic vacuolation, but the bronchoalveolar epithelium did not show signs of cellular degeneration or ciliocytophthoria (Lopez et al. 1987).

In similar experiments Green and co-workers (1991) exposed male Fisher 344 rats to 200 and 300 ppm hydrogen sulfide for 4 hours, and evaluated the impact on lung lavage fluid surface tension, protein concentrations, and lactate dehydrogenase activity. These authors found significant increases in protein concentrations and lactate dehydrogenase activity at both exposure concentrations, but a significant change in the surface tension of lavage fluids only at the high dose. Focal area of perivascular edema and proteinaceous material in the alveoli were also seen in the lungs of the exposed animals.

Histopathological changes have been reported in the nasal cavity of Fisher-344 rats (Lopez et al. 1988b). Male rats were exposed to 0, 10,200, or 400 ppm hydrogen sulfide for 4 hours. Necrosis and exfoliation of the respiratory and olfactory mucosal cells were observed 1 hour postexposure at concentrations >200 ppm; by 20 hours postexposure, the respiratory epithelium was covered by a layer of deeply basophilic cells containing mitotic figures and severe inflammatory response was noted. The necrosis ultimately ulcerated the respiratory epithelium causing exposure of the basement membrane (Lopez et al. 1988b). Although some histological changes were observed at 10 and 200 ppm hydrogen sulfide, no dose response was evident; it appears that a concentration >200 ppm is necessary to induce these lesions (Lopez et al. 1988b).

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Cytochrome c oxidase activity in lung mitochondria of Fisher-344 rats was significantly decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) hydrogen sulfide compared to controls after a 4-hour exposure (Khan et al. 1990). Cytochrome c oxidase activity had returned to normal for animals exposed to 200 ppm, but not for those exposed to 400 ppm, by 24 hours postexposure. Succinate oxidase activity was reduced at 200 ppm (40%) and 400 ppm (63%) but was not affected at 50 ppm (Khan et al. 1990).

Significant decreases in numbers of viable pulmonary alveolar macrophages were noted in the lung lavage fluid of male rats exposed for 4 hours to 400 ppm hydrogen sulfide (Khan et al. 1991). This study also showed complete abolition of zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages in animals exposed to 200 or 400 ppm. No changes were noted after exposure to 50 ppm hydrogen sulfide.

Histological changes were characterized in the lungs of male Fischer-344 rats exposed to 83 or 439 ppm for 4 hours (Lopez et al. 1988a). At the low dose, mild perivascular edema was found, but at the high dose, numerous changes were observed, including: severe but transient pulmonary edema and fibrocellular alveolitis in proximal alveoli; cytoplasmic blebs in the alveolar endothelium; increased numbers of mitotic figures in the bronchiolar epithelium; minor changes in the alveolar epithelium; and necrosis of the ciliated bronchiolar cells. Moderate-to-massive pulmonary edema was evident in male Fisher-344 rats exposed to 375 or 399 ppm for 4 hours (Prior et al. 1990), and slight pulmonary congestion was found in male Wistar rats exposed to 75 ppm hydrogen sulfide for 1 hour (Kohno et al. 1991).

The effects of intermediate-duration exposures to hydrogen sulfide have been examined in rats, mice, and pigs. Respiratory effects were not observed in Fischer-344 (CIIT 1983b) or Sprague-Dawley (CIIT 1983c) rats exposed to hydrogen sulfide at concentrations up to 80 ppm 6 hours/day, 5 days/week, for 90 days. In contrast to rats, inflammation of the nasal mucosa described as minimal to mild was observed in $B6C3F_1$ mice exposed to hydrogen sulfide at 80 ppm (CRT 1983a). Respiratory effects were not observed at 30.5 ppm. Based on a NOAEL of 30.5 ppm for respiratory effects in mice observed in the CIIT 1983a study, an intermediated MRL of 0.03 ppm was derived. The NOAEL is adjusted for intermittent exposure and the human equivalent concentration NOAEL ($NOAEL_{[HEC]}$) is calculated using the methodology of EPA (1994b) for a "gas:respiratory" effect. An uncertainty factor of 30 is then applied, 3 for extrapolating from animals to humans and 10 for human variability.

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Three crossbred pigs of unspecified sex were continuously exposed to 0 or 8.5 ppm hydrogen sulfide in inhalation chambers for 17 days (Curtis et al. 1975). No significant changes in body weight gain and no histopathological changes in the respiratory tract (including turbinates, trachea, and lungs) were noted. This study is limited by the number of animals used and because only one exposure concentration was used.

Cardiovascular Effects. Cardiovascular effects have been noted after acute exposures to high concentrations of hydrogen sulfide via inhalation (Arnold et al. 1985). Slight blood pressure increases were noted in several workers exposed to hydrogen sulfide in a pelt room, however, their electrocardiograms (EKGs) were normal (Audeau et al. 1985). In other instances of hydrogen sulfide poisoning that occurred after a short exposure to high concentrations, no changes in blood pressure were noted despite other cardiac irregularities (Ravizza et al. 1982). Hemodynamic instability was noted in one of two men who survived acute exposure to an unknown concentration of hydrogen sulfide and also swallowed large amounts of manure after entering a partially drained liquid manure pit (Osbern and Crapo 1981). Sinus tachycardia has been noted in men who completely recovered after exposure to hydrogen sulfide (Peters 198 1; Ravizza et al. 1982). Supraventricular tachycardia and left bundle block was noted in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution dumped onto acid waste material; the effects were temporary (Stine et al. 1976). Extreme tachycardia and hypotension were noted in a woman who attempted to clean a well with muriatic acid and was exposed to an unknown concentration of hydrogen sulfide gas; hypertension was noted in a man exposed during this same incident (Thoman 1969).

EKGs taken on two workers about 2.5 hours after an acute exposure to hydrogen sulfide showed cardiac arrhythmias (Krekel 1964). The workers were exposed for <5 minutes after a spill of sodium sulfide that broke down to release hydrogen sulfide. In one individual, a negative P wave indicating a substitute rhythm was noted, while in the other individual a continuous arrhythmia due to atria1 flutter was found. EKGs for both men had returned to normal within 24 hours.

No adverse cardiovascular effects were found when healthy male volunteers were exposed to hydrogen sulfide concentrations up to 5 ppm for more than 16 minutes after graded exercise performed to exhaustion (Bhambhani and Singh 1991). A study that examined the effects of inhalation of 5 ppm hydrogen sulfide on physiological parameters found no changes in heart rate, blood pressure, percent hemoglobin saturation, perceived exertion, or other parameters in healthy male and female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). A subsequent study examining the effects of inhaling 10 ppm

hydrogen sulfide during two 30-minute sessions of submaximal exercise found no significant changes in cardiovascular responses under these conditions (Bhambhani et al. 1997).

In a retrospective epidemiologic study using hospital discharge data from 198 l-l 990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. A significant increase in incidence was found for diseases of the circulatory system (SIR = 1.05; p = 0.001) among Rotorua residents as compared to all other New Zealand residents. Although previous monitoring information from Rotorua in 1978 showed a median concentration of hydrogen sulfide of 20 $\mu g/m^3$, with 35% of the measurements over 70 $\mu g/m^3$and 10% over 400 $\mu g/m^3$ (Bates et al. 1997), the lack of monitoring information concurrent with these data precludes conclusions with regard to a causal relationship between circulatory system disease and hydrogen sulfide exposures.

A 1.5-hour inhalation exposure of mixed breed rabbits to airborne concentrations of 72 ppm of hydrogen sulfide resulted in ventricular repolarization, while a 5-day, 0.5hour/day exposure to this concentration resulted in cardiac arrhythmia (Kosmider et al. 1967). Histochemical staining of the myocardial cells revealed a reduction in adenosine tri-phosphate (ATP) phosphohydrolase and NADPH, oxidoreductase (Kosmider et al. 1967). Cardiac arrhythmia, suggestive of a stimulus transmission disorder, was observed in male Wistar rats exposed to 75 ppm hydrogen sulfide for up to 60 minutes (Kohno et al. 1991). Heart rates in these animals were also 10-27% less than controls during exposure and up to 1 hour postexposure (Kohno et al. 1991). A temporary yet marked increase in blood pressure was noted in male Wistar rats exposed to 100-200 ppm hydrogen sulfide for 1 hour (Higuchi and Fukamachi 1977). No treatment-related histopathological effects were noted on the cardiovascular system of Fisher-344 or Sprague-Dawley rats or $B6C3F_1$, mice exposed via inhalation to time-weighted-average (TWA) concentrations of 10.1,30.5, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Gastrointestinal Effects. Nausea and vomiting have been noted in several cases of human inhalational hydrogen sulfide poisoning (Allyn 1931; Audeau et al. 1985; Deng and Chang 1987; Krekel l964; Osbern and Crapo 1981; Thoman 1969).

In two evaluations of the acute health effects associated with communities experiencing episodes of high emissions, significant increases in the reporting of nausea as a symptom have been reported (Haahtela et al. 1992; Marttila et al. 1995). In the first study, increased emissions from a pulp mill resulted in increased

concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 µg/m^3 (96.4 ppb) and the 24-hour averages for the 2 days were 35 and 43 µg/m^3 (25 and 31 ppb). Following the high exposure, and then after a low exposure period (hydrogen sulfide level of 0.1 to 3. µg/m^3 [0.07-2.5 ppb] for 4 hours), community responses were evaluated with a questionnaire. In this comparison the concentration of sulfur dioxide was the same. In a study, Marttila et al. (1995) compared community responses using 6 consecutive questionnaires after 3 predefined levels of exposure. The three exposure levels were expressed as µg/m^3 of total reduced sulfur (TRS) as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <l0 µg/m^3), (medium 10-30 µg/m^3), and high exposure (>30 µg/m^3). While the study found a dose-related increase in the probability of both nasal and pharyngeal symptoms, the increase in reports of nausea were significant only with the highest level of exposure. Interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that hydrogen sulfide represented two-thirds of the TRS (Marttila et al. 1994a). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by each of the questionnaires, indicated that only sulfur dioxide appeared to co-vary with TRS.

No treatment-related histopathological changes were detected in the gastrointestinal tract of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed via inhalation TWA concentrations of 10.1,30.5, or 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No gastrointestinal effects were reported in crossbred pigs exposed to 8.5 ppm hydrogen sulfide for 24 hours/day for 17 days (Curtis et al. 1975).

Hematological Effects. The cyanosis that has been reported in a number of cases of accidental exposure to hydrogen sulfide is believed to result from respiratory distress (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Peters 1981; Ravizza et al. 1982; Stine et al. 1976; Tvedt et al. 1991a, 1991b).

Complete blood counts were normal in four individuals overcome by unknown concentrations of hydrogen sulfide gas in a pelt room (Audeau et al. 1985). Percent hemoglobin saturation was unchanged by inhalation of either 5 ppm hydrogen sulfide by volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994), or 10 ppm hydrogen sulfide during two 30 minute sessions of submaximal exercise (Bhambhani et al. 1997).

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Workers who were sometimes exposed to airborne concentrations of >20 ppm hydrogen sulfide did not have any changes in hematological parameters (Ahlborg 1951). Pulp industry workers (n=17) exposed to 8-hour TWA concentrations of 0.05-5.2 ppm hydrogen sulfide had no signs of clinical anemia (Tenhunen et al. 1983). Jappinen and Tenhunen (1990) examined blood sulfide concentration and changes in heme metabolism at 2-hours, 1 -week, and 1 -month post-hydrogen sulfide poisoning in 6 cases of occupational exposure. Decreased delta-aminolaevulinic acid synthase activities and erythrocyte protoporphyrin concentrations were noted at the 2-hour and 1 -week time periods, but not to the level of significance, and there was no change in heme synthase activity.

No treatment-related changes in hematological parameters were noted in Fisher-344 or Sprague-Dawley rats or B6C3F_1 mice exposed by inhalation to TWA concentrations of 10.1,30.5, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Musculoskeletal Effects. In a series of reports characterizing the responses of healthy volunteers to low level, short-term exposures to hydrogen sulfide, Bhambhani and his colleagues (Bhambhani and Singh 199 1; Bhambhani et al. 1994, 1996a, 1996b, 1997) concluded that exposures to 5 or 10 ppm hydrogen sulfide resulted in increases in blood lactate concentrations and a decrease in muscle citrate synthase activity indicative of an inhibition of the aerobic capacity of exercising muscle. Men appeared to be more sensitive to this effect, showing a small response at 5 ppm where women did not show an effect until the 10 ppm level (Bhambhani et al. 1996b, 1997).

No treatment-related histopathological changes were detected in the skeletal muscle, bone marrow, or bone of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10.1,30.5, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Hepatic Effects. Increases in unspecified liver enzyme activities were noted in some of 221 persons exposed by inhalation to hydrogen sulfide (Burnett et al. 1977). No baseline for these effects was available and they were not quantified.

No changes in serum protein, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT; AST), or alkaline phosphatase activities were noted in Sprague-Dawley rat dams exposed to 20, 50, or 75 ppm of hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21 (Hayden et al.

1990a). Maternal liver cholesterol levels were increased in Sprague-Dawley dams exposed to 75 ppm, but not 50 ppm, for 7 hours/day from gestation day 6 to postpartum day 21 (Hayden et al. 1990b).

No treatment-related histopathological changes were detected in the livers of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10.1,30.5, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No gross or histopathological lesions were found in the livers of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Renal Effects. Blood urea nitrogen and serum electrolyte levels were normal in several individuals overcome by unknown concentrations of hydrogen sulfide gas in a pelt room (Audeau et al. 1985). One of these four patients had protein and blood in the urine initially, which was not detected upon later testing. Albumin and some granular casts were noted in the urine in another patient, but these findings were transient (Audeau et al. 1985).

Fischer-344 and Sprague-Dawley rats as well as B6C3F_1 mice were exposed to TWA concentrations of 10.1, 30.5, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No treatment-related histopathological changes were detected in the kidneys of these animals and urinalysis findings were negative, indicating no renal effects due to hydrogen sulfide exposure. No gross or histopathological lesions were found in the kidneys of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to hydrogen sulfide.

No treatment-related histopathological changes were detected in the pituitary, adrenal, thyroid, or parathyroid glands of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10.1, 30.5, or 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Dermal Effects. Six men lost consciousness after acute hydrogen sulfide exposure; one with probable exposure to 8-16 ppm had peeling facial skin (Tvedt et al. 1991a, 1991b).

No treatment-related histopathological changes were detected in the skin of Fischer-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed to TWA concentrations of 10.1, 30.5, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). Slate-grey skin discoloration and erythema were noted in rabbits exposed to unspecified concentrations of hydrogen sulfide for 2 hours (Laug and Draize 1942).

Ocular Effects. Ocular effects reported after inhalation exposure are believed to have resulted from direct eye contact with hydrogen sulfide gas. Hydrogen sulfide gas is an eye irritant. Keratoconjunctivitis (sometimes with subsequent infection), punctate cornea1 erosion, blepharospasm, lacrimation, and photophobia have developed in individuals exposed to brief high-level concentrations of hydrogen sulfide gas (Ahlborg 1951; Luck and Kaye 1989). Hemorrhagic keratoconjunctivitis and subconjunctival hemorrhage were reported in cases of near-lethal poisoning to unknown concentrations of hydrogen sulfide (Deng and Chang 1987; Stine et al. 1976). A retrospective study of 250 Canadian workers who submitted workers' compensation claims for hydrogen sulfide exposure found that 18% had developed conjunctivitis, which in some cases persisted for several days (Arnold et al. 1985). Stinging has been reported in acute occupational hydrogen sulfide poisoning (Audeau et al. 1985). None of these reports of ocular exposure suggested that permanent eye effects may occur (Ahlborg 195 1; Arnold et al. 1985; Audeau et al. 1985; Deng and Chang 1987; Luck and Kaye 1989; Stine et al. 1976). People exposed to hydrogen sulfide, methyl mercaptan, and methyl sulfides while living in a community around a paper mill reported 12 times more eye irritation than people without exposure (Jaakkola et al. 1990). These effects were observed at mean annual hydrogen sulfide exposures estimated at 6 $\mu g/m^3$ (4.3 ppb). However, the ocular symptoms that were reported may have been due to exposure to peak concentrations of hydrogen sulfide (daily peaks as high as 100 $\mu g/m^3$; 70 ppb) and not annual mean concentrations, or may have been have been due to co-exposure to methyl mercaptan and methyl sulfides. Methyl mercaptan is also an eye irritant (NIOSH 1997) and it was also present at an annual mean concentration of 2-5 $\mu g/m^3$ with the highest daily average concentration being 50 $\mu g/m^3$ (Jaakkola et al. 1990).

In a retrospective epidemiologic study using hospital discharge data from 198l-1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but the authors indicate concerns that exposures to hydrogen sulfide and/or mercury from geothermal sources could have health impacts. In their previous work it was indicated that the most reliable monitoring information for hydrogen sulfide in the area

came from a monitoring exercise in 1978 that found a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3 (Bates et al. 1997). On the basis of hospital discharge data, significant increases in incidence were found for diseases of the nervous system and sense organs (SIR = 1.11; p <0.001) among Rotorua residents as compared to the rest of New Zealand. When incidence rates were examined for minor disease groupings within this group of nervous system and sense organ diseases, significantly increased risks were seen for other disorders of the eye and adnexa (SIR = 1.12; p<0.001). At the level of individual diseases, statistically significant incidence ratios were found for cataract (SIR = 1.26; p <0.001), disorders of the conjunctiva (SIR = 2.09; p <0.001), and disorders of the orbit (SIR = 1.69; p = 0.005). The effect of hydrogen sulfide on the eye is of considerable importance because ocular effects occur at concentrations that provide no other observable systemic effect (NIOSH 1977a).

Ocular irritation has also been noted after animals were exposed to hydrogen sulfide. Epiphora was noted in Fischer-344 rats exposed to 400 ppm, but not 200 ppm, of hydrogen sulfide for 4 hours (Lopez et al. 1988b). Eye irritation was noted in guinea pigs exposed to 20 ppm of hydrogen sulfide for 20 days, 1 hour/day (Haider et al. 1980). No ocular lesions were found upon microscopic examination of the eyes of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide for 17 days, 24 hours/day (Curtis et al. 1975).

No treatment-related histopathological changes were detected in the eyes of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10.1,30.5, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to hydrogen sulfide.

Pregnant Sprague-Dawley rats exposed to 100 or 150 ppm hydrogen sulfide on gestation days 6-20 showed decreased body weight gains which only reached significance at the higher dose. Absolute weight gain (i.e., minus the gravid uterine weight) was significantly depressed at both of these doses. Exposure at 50 ppm hydrogen sulfide had no effect on body weight gain or on absolute weight gain (Saillenfait al. 1989). No effects on body weight were noted in Sprague-Dawley rats exposed to 50 ppm of hydrogen sulfide 5 days/week, for 25 weeks (Gagnaire et al. 1986). No treatment-related body weight changes were noted in Fischer-344 rats exposed to TWA airborne concentrations of 10.1,30.5, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983b). However, when Sprague-Dawley rats were exposed on the same regimen, females at 80 ppm showed a significant (10%) decrease in body weight at the end of the

study compared to controls, which was not evident at 30.5 ppm (CIIT 1983c). At 80 ppm, the body weight of males was significantly less (8%) than controls during weeks 1-3, but the final body weight differences were not significant (CIIT 1983c). Similarly, B6C3F_1 mice of both sexes exposed to TWA concentrations of 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days showed decreases in body weight of 7-14% compared to controls; these changes were not observed at 30.5 ppm (CIIT 1983a). No body weight changes were found in crossbred pigs exposed to 8.5 ppm hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Metabolic Effects. Severe metabolic acidosis developed in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution dumped onto acid waste material (Stine et al. 1976). Blood lactate concentrations were significantly increased (65%) compared to controls during exercise in men exposed to 5 ppm hydrogen sulfide for more than 16 minutes (Bhambhani and Singh 1991) but not at 2 ppm. Additional studies by the same group (Bhambhani et al. 1994, 1996b) exposed both men and women to 5 ppm hydrogen sulfide during 30 minutes of exercise and failed to observe significant increases in lactate concentrations but did see a decrease in muscle citrate synthase in men, suggesting that aerobic metabolism was being compromised at this level of exposure.

In a subsequent study Bhambhani et al. (1997) observed significant increases in blood lactate concentrations in male and female volunteers exposed to 10 ppm hydrogen sulfide, although there was not a significant change in the activities of muscle lactate dehydrogenase, citrate synthase, or cytochrome oxidase.
In Sprague-Dawley rat dams exposed to 20,50, or 75 ppm of hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21, blood glucose levels were increased about 50% at all exposure concentrations (Hayden et al. 1990a).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after inhalation exposure to hydrogen sulfide.

No treatment-related histopathological changes were found in the spleen or lymph nodes of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10.1, 30.5, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). Pulmonary alveolar macrophage

function was studied using lavage fluid from Fischer-344 rats exposed for 4 hours to 50,200, or 400 ppm hydrogen sulfide (Khan et al. 1991). Although the number of pulmonary alveolar macrophage cells was not influenced by hydrogen sulfide exposure, the number of viable cells was significantly decreased at 400 ppm. When the pulmonary alveolar macrophage cells were treated with Zymosan to stimulate respiration rates, it was found that there was no stimulation of respiration in cells from animals exposed to 200 or 400 ppm; these rates were significantly different from controls and were approximately equal to basal cell levels (Khan et al. 1991).

The highest NOAEL values and all reliable LOAEL values for immunological effects in rats and mice exposed in acute- and intermediate-duration studies are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.4 Neurological Effects

Acute human exposure to hydrogen sulfide can result in nausea, headaches, delirium, disturbed equilibrium, poor memory, neurobehavioral changes, olfactory paralysis, loss of consciousness, tremors, and convulsions. Fatigue, poor memory, dizziness, and irritability have been observed in workers chronically exposed to hydrogen sulfide (Beauchamp et al. 1984).

Available information on the neurotoxic effects of acute exposures to hydrogen sulfide in humans comes primarily from case reports. In most instances, exposure concentrations were either unknown or estimated. Exposure durations were brief and varied from several minutes to 3 hours. Loss of consciousness has frequently been reported with acute hydrogen sulfide exposure. Three men accidentally exposed to hydrogen sulfide concentrations in excess of 250 ppm quickly became unconscious (McDonald and McIntosh 1951). Loss of consciousness has also been observed in individuals acutely exposed to estimated concentrations of 50-2,000 ppm hydrogen sulfide (Deng and Chang 1987; Krekel 1964; Milby 1962; Spolyar 1951). Other described neurological effects in the case reports include disturbed equilibrium, nausea, headache, poor memory, insomnia, irritability, delirium, severe vertigo, unusual sweating, neuropsychological symptoms, convulsions, and tremors (Arnold et al. 1985; Krekel 1964). While deaths were often noted, there were cases in which individuals survived and had complete neurological recovery (Deng and Chang 1987; Krekel 1964; Osbern and Crapo 1981; Ravizza et al. 1982). In a study of the possible effects of exposure to low concentrations of hydrogen sulfide, 3/ 10 asthmatic volunteers complained of headache after being exposed in a sealed chamber to 2 ppm hydrogen sulfide for 30 minutes (Jappinen et al. 1990).

2. HEALTH EFFECTS

A few case reports have described permanent or persistent neurological effects in humans following acute inhalation exposure to high concentrations of hydrogen sulfide. One patient developed symptoms of frontal headaches, irritability, poor concentration ability and attention span, and deficits of cortical function tests, including verbal abstraction, attention, and short-term retention 1 month after accidental exposure to unspecified concentrations of hydrogen sulfide (Stine et al. 1976). All effects except headaches resolved by 2 months after the accident. A 5-10-year follow-up re-examination of several individuals who became unconscious after exposure to unspecified concentrations of hydrogen sulfide revealed permanent neurological symptoms (Tvedt et al. 1991 a, 1991b) including vision and memory impairment; rigid movements; reduced motor function; slight tremor; ataxia; psychosis; abnormal learning, retention, and motor function; and slight cerebral atrophy. The probable exposure concentration in 1 of the patients may have exceeded 200 ppm (as measured 2.5 hours after exposure). Divergent reports of the risk of permanent neurological damage due to hydrogen sulfide may result from lack of follow-up after hospital discharge (Tvedt et al. 1991 b). Permanent neurologic damage including effects on balance, vibration sense, and impaired verbal and visual recall were observed in 1 man exposed to a very high concentration (14,000 ppm) of hydrogen sulfide (Kilbum 1993). In another case report, a worker who suffered ‘knockdown’ and presented in a coma, remained in a coma through standard treatment (i.e., sodium nitrite) underwent several treatments with hyperbaric oxygen, and became responsive to simple commands by day 5. However, at the time of discharge, an extensive head injury assessment found effects on speech, attention span, insight and ability to communicate, as well as a marked impact on visual memory and the ability to acquire, retain, and recall new information. These effects had not resolved by 12 and 18 months after exposure (Snyder et al. 1995). In a somewhat similar scenario, Schneider et al. (1998) describe a case in which another worker lost consciousness when he descended into a 27 foot pit that was part of a sewer construction project. He was overcome by hydrogen sulfide fumes (concentration not specified), fell from a ladder from an unspecified height, and was subsequently removed in a coma and transported to a local trauma center. At the emergency room (and potentially at the site) the patient experienced seizure activity. A body computed tomography (CT) scan showed pulmonary edema while a head CT scan was normal. The patient was transferred to a hyperbaric medicine unit and started on hyperbaric oxygen treatments (starting approximately 10 hours postepisode).

Five days later he recovered consciousness and by seven days his status had improved enough to discontinue hyperbaric oxygen treatments. He was able to feed himself and move with assistance, but had impaired language, memory and attention, and appeared agitated and restless. Over the course the next four years the patient was evaluated on a variety of occasions. He continued to show a constellation of deficits, which even four years later, included problems with general cognition, motor function, and cognitive function;

some of these symptoms appeared to be alleviated through a combined treatment with fairly high doses of Ritalin and Cyclert drugs, which enhance dopaminergic functioning.

In a case control study of 16 subjects who had been exposed for minutes, hours, or years to hydrogen sulfide, Kilburn (1997) found evidence of permanent neurobehavior impairment in exposed individuals when compared to 353 controls matched for sex, age, and years of education. A large battery of tests was used to evaluate these individuals, including a detailed self-administered questionnaire, complete physical and clinical screen neurologic examinations, as well as a series of neurophysiologic and neuropsychologic tests. Among those who had chronic low-dose exposure, the most sensitive tests were those evaluating balance, simple reaction time, left visual field, and verbal recall. The group exposed to hydrogen sulfide for hours showed additional defects, including impacts on a variety of neuopsychological tests although remote memory remained intact. The group that experienced momentary knock-down exposure had an even larger suite of deficit cognitive functions, leading the study author to conclude that ". . .brief high doses were devastating, whereas protracted low doses showed effects on the more sensitive tests."

A 20-month-old child was exposed for nearly 1 year to >0.6 ppm hydrogen sulfide and other emitted chemicals from a coal mine (Gaitonde et al. 1987). Symptoms included ataxia, choreoathetosis, dystonia, and inability to stand. Computed tomography (CT) scan of the brain showed bilateral areas of low density in the region of both basal ganglia and surrounding white matter. Neurophysiological investigations of electroencephalography, visual evoked responses, brain stem evoked responses, and peripheral nerve conduction studies were normal. The child's condition improved spontaneously, shortly after hospital admission; after 10 weeks, ataxia had resolved and the choreoathetoid movements were reduced. A repeat brain scan showed complete resolution of abnormalities. The relationship of these complaints to low-level hydrogen sulfide exposure is unclear.

Neurological effects resulting from chronic-duration exposure to hydrogen sulfide in the shale industry have been reported (Ahlborg 1951). Symptoms observed in workers exposed to daily concentrations of hydrogen sulfide that often exceeded 20 ppm included fatigue, loss of appetite, headache, irritability, poor memory, and dizziness. The frequency of fatigue increased with length of employment and the degree of hydrogen sulfide exposure.

In the South Karelia air pollution study, discussed in more detail under respiratory effects, all of the reports found significant increases in the incidence of headaches or migraines in polluted communities when

compared to nonpolluted communities (Jaakkola et al. 1990; Marttila et al. 1994b; Marttila et al. 1995; Partti-Pellinen et al. 1996); however, only in the most recent study did this finding achieve significance. Using a cross-sectional, self-administered questionnaire, this report (Partti-Pellinen et al. 1996) evaluated the increased risk of headache or migraine in adults in a slightly polluted and a reference community. In the polluted community, the mean annual TRS concentrations were 2-3 μg/m^3, the 24 hour concentrations varied between O-56 μg/m^3, and the maximum l-hour concentration was 155 μg/m^3; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 μg/m^3, the 24-hour concentrations varied between 0 and 24 μg/$m^3$and the maximum 1 -hour concentration was 152 μg/m^3; in the reference community the mean sulfur dioxide level was 1 μg/m^3, and the maximum 1 -hour concentration was 30 μg/m^3. The residents of the polluted community showed a significantly increased risk of headache both during the previous 4-week period (OR = 1.83; 95% CI = 1.06-3.15) and the preceding 12 months (OR = 1.70; 95% CI = 1 .01-2.64), when compared to the residents of the reference community, even after adjusting for differences in age, gender, smoking, history of allergic diseases, education, and marital status between the two communities.

In a retrospective epidemiologic study using hospital discharge data from 198 l-l 990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. Although no information on hydrogen sulfide levels was presented in this report, the authors' previous work indicated that a monitoring exercise in Rotorua in 1978 found a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements >70 μg/$m^3$and 10% >400 μg/m^3; additionally, elevated concentrations of mercury had previously been found in the hair of residents (Bates et al. 1997). Significant increases in incidence were found for diseases of the nervous system and sense organs (SIR = 1.11; p <0.001) among Rotorua residents as compared to the rest of New Zealand residents. When the data were stratified by gender and ethnicity, the increased risks remained significant for all but non-Maori men. When incidence rates were examined for minor disease groupings within nervous system diseases, significantly increased risks were seen for other disorders of the central nervous system (SIR = 1.22; p <0.001), and disorders of the peripheral nervous system (SIR = 1.35; p<0.001). At the level of individual diseases, statistically significant incidence ratios were found for infant cerebral palsy (SIR = 1.42; p = 0.02), migraine (SIR = 1.40; p = 0.002), other conditions of the brain (SIR = 2.50; p<0.001), mononeuritis of the upper limbs and mononeuritis multiplex (SIR = 1.47; p <0.001), and mononeuritis of the lower limbs (SIR = 2.06; p <0.001).

Rabbits exposed to 72 ppm of hydrogen sulfide for 1.5 hours lost consciousness (Kosmider et al. 1967). Guinea pigs exposed daily to 20 ppm of hydrogen sulfide for 11 days developed fatigue, somnolence, and dizziness (Haider et al. 1980). Neurochemical analyses revealed decreased cerebral hemisphere and brain stem total lipids and phospholipids. Rats exposed to 800 ppm of hydrogen sulfide for 20 minutes lost consciousness (Beck et al. 1979). Lethargy was observed in rats following exposure to 400 ppm of hydrogen sulfide for 4 hours (Lopez et al. 1988b).

Male Wistar rats were exposed to average concentrations of 100-200,200-300,300-400, or 400-500 ppm hydrogen sulfide; at 200-300 ppm, a decreased response rate in a discriminated avoidance task was observed (Higuchi and Fukamachi 1977). Except at the highest concentrations tested, the response rates and percent avoidances recovered rapidly when ventilation with clean air was provided, although even at 400-500 ppm, they were almost normal the following day (Higuchi and Fukamachi 1977). When these same animals were tested for Sidman-type conditioned avoidance response at response-shock intervals of 10 or 30 seconds, an inverse relationship between hydrogen sulfide concentration and response rate was noted (Higuchi and Fukamachi 1977); this effect dissipated when exposure stopped.

Female NMRI mice were exposed to 100 ppm of hydrogen sulfide for 2 hours at 4-day intervals; excitement was observed (Savolainen et al. 1980). Exposure also resulted in decreased cerebral ribonucleic acid (RNA), decreased erotic acid incorporation into the RNA fraction, and inhibition of cytochrome oxidase. An increase in the glial enzyme marker, 2 ‘,3 ‘-cyclic nucleotide-3 ‘-phosphohydrolase, was seen. Neurochemical effects have been reported in other studies. Decreased leucine uptake and acid proteinase activity in the brain were observed in mice exposed to 100 ppm hydrogen sulfide for 2 hours (Elovaara et al. 1978). Inhibition of brain cytochrome oxidase and a decrease in erotic acid uptake were observed in mice exposed to 100 ppm hydrogen sulfide for up to 4 days (Savolainen et al. 1980).

The intermediate-duration effects of hydrogen sulfide on neurological function were examined by the measurement of motor and sensory nerve conduction velocities of the tail nerve or morphology of the sciatic nerve (Gagnaire et al. 1986). Male Sprague-Dawley rats were exposed to 0 or 50 ppm hydrogen sulfide for 5 days a week, for 25 weeks. The study authors did not report the duration of exposure to hydrogen sulfide per day. No neurotoxic effects were observed in the rats.

Neurologic function and neuropathology were evaluated in Sprague-Dawley rats exposed to 0, 10.1, 30.5, or 80.0 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983c). Neurological function

evaluation included: an assessment of posture; gait; tone of facial muscles; pupillary, palpebral, extensor thrust; and crossed-extensor thrust reflexes. Besides routine neuropathologic examinations, special studies included an examination of teased fibers from muscular and sural branches of the tibia1 nerve together with specimens from cervical and lumbar spinal cord. Absolute brain weights were decreased (5%) in male rats exposed to 80 ppm hydrogen sulfide in this study; however, there were no treatment-related effects on neurological function or neuropathology.

No signs of neurotoxicity were noted in a similar study in which Fischer-344 rats were exposed to 0, 10.1, 30.5, or 80.0 ppm hydrogen sulfide for 90 days (CIIT 1983b). Likewise, no treatment-related neurological effects were observed in male and female B6C3F_1 mice exposed to 0, 10.1, 30.5, or 80.0 ppm hydrogen sulfide for 90 days (CIIT 1983a).

The highest NOAEL values and all reliable LOAEL values for neurological effects in rats, guinea pigs, mice, and rabbits from acute- or intermediate-duration studies are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

There is some evidence that suggests that exposure to hydrogen sulfide may be associated with an increase in the rate of spontaneous abortion. Hemminki and Niemi (1982) examined the spontaneous abortion rate in relationship to maternal and paternal occupation and residential environmental pollution in an industrial community in Finland. Women who were employed in rayon textile and paper products jobs had an increased rate of spontaneous abortions ($p<0.10$), as did women whose husbands worked in rayon textile or chemical processing jobs. Pollutants examined were sulfur dioxide, hydrogen sulfide, and carbon disulfide. Only exposure to hydrogen sulfide resulted in an increase in spontaneous abortions in the more highly-exposed population; however, the difference was not large enough to be significant. In a recent retrospective study of spontaneous abortions in a large population of women working in the petrochemical industry in China, Xu et al. (1998) reported a significantly increased risk of spontaneous abortion with frequent exposure to petrochemicals (odds ratio of 2.7; 95% CI 1.8-3.9). When the risk associated with exposure to specific chemicals was examined, exposure to hydrogen sulfide was found to have an odds ratio of 2.3 (95% CI = 1.2-4.4).

No treatment-related histopathological changes were found in male or female reproductive organs of Fischer-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10.1, 30.5, or 80 ppm

hydrogen sulfide for 6 hours/day, 5 days/week. for 90 days (CIIT 1983a, 1983b, 1983c). When Sprague-Dawley rats were exposed to 0,20,50, or 75 ppm hydrogen sulfide for 7 hours/day on gestation days 6-2 1, a dose-dependent increase in parturition time and difficult delivery was noted in 6/19 exposed animals from all concentrations compared to l/17 controls (Hayden et al. 1990b). No threshold for the effect on parturition time could be determined. However, parturition time was variable (means of 82.5-124 minutes) among control groups and was not analyzed statistically. In addition to the impact on delivery, there was a significant increase in cholesterol content of the livers of the dams, but not the pups, at 75 ppm (Hayden et al. 1990b).

The highest NOAEL values for reproductive effects in rats and mice from intermediate-duration studies are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to hydrogen sulfide.

No changes in serum protein, LDH, SGOT, or alkaline phosphatase activities were noted in the offspring of Sprague-Dawley rats exposed to 20,50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21 (Hayden et al. 1990a). No effects on blood glucose were noted in the offspring, although glucose levels were increased by about 50% in dams at all exposure concentrations on postnatal day 21 (Hayden et al. 1990a). In a second study, these authors (Hayden et al. 1990b) found a dose-related increase in parturition time in animals exposed to 20,50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 6 until postpartum day 21. The study also showed developmental delays in pinna attachment and hair growth, but these effects were not dose related.

No fetal effects were noted in a dose range-finding developmental study in which pregnant Sprague-Dawley rats were exposed to 150 ppm hydrogen sulfide on gestation days 6-20, despite body weight loss in the dams (Saillenfait et al. 1989).

An examination of Purkinje cells from Sprague-Dawley rat pups exposed to 20 or 50 ppm hydrogen sulfide for 7 hours/day from gestation day 5 through postpartum day 21 showed severe alterations in the architecture and growth characteristic of the Purkinje cell dendritic fields compared to controls (Hannah and Roth 1991).

The study did not mention whether any maternal effects were observed; however, the authors did indicate that "these findings suggest that developing neurons exposed to low concentrations of hydrogen sulfide are at risk of severe deficits." Two studies by Hannah et al. (1989, 1990) examined the effects of prenatal exposure to hydrogen sulfide on amino acid levels in the brain. In the first study, pregnant Sprague-Dawley rats were exposed to 75 ppm hydrogen sulfide for 7 hours/day, from postcoitus day 5 to postpartum day 2 1 (Hannah et al. 1989). Aspartate, glutamate, and GABA in the cerebrum and cerebellum were significantly reduced (about 20%) compared to controls by postpartum day 21. Taurine levels of the offspring were initially 25% higher than controls but had returned to control range by postpartum day 21; taurine levels were not measured in dams. In the 1990 study, pregnant Sprague-Dawley rats were exposed to 50 ppm hydrogen sulfide for 7 hours/day, from postcoital day 6 to postpartum day 21 (Hannah et al. 1990). In this study, maternal taurine levels were determined on parturition and on postpartum day 21. Taurine in maternal plasma was 30% higher than controls; taurine levels were not determined in offspring, so relating these levels to high taurine levels found in offspring in the 1989 study is speculative.

Further investigation into the developmental neurological effects of hydrogen sulfide was undertaken by Skrajny et al. (1992). Pregnant Sprague-Dawley rats were exposed to 20 or 75 ppm hydrogen sulfide 7 hours/day from gestation day 5 to postpartum day 21; separate control groups were used for each exposure level. Exposure to 20 ppm caused significant increases compared to controls in serotonin levels in the frontal cortex on postpartum day 21. Exposure to 75 ppm hydrogen sulfide caused significant increases compared to controls in levels of serotonin in the cerebellum and cortex on postpartum days 14 and 21. Norepinephrine levels were significantly increased compared to controls at 75 ppm in the cerebellum and the frontal cortex. At 20 ppm, norepinephrine levels were below control levels by days 14 and 21, and in the cerebellum, levels fluctuated but were normal by postpartum day 21 (Skrajny et al. 1992). In a subsequent study using the same exposure regimen (i.e., between day 5 postcoital until day 21 postnatal), but following the monoamine levels in various regions of the brain up to 60 days postnatal, Roth et al. 1995 found that the alterations of monoamine levels observed at day 2 1 postnatal (the last day of exposure) gradually returned to control values by day 45.

The highest NOAEL and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxicity in humans after inhalation exposure to hydrogen sulfide.
No mutagenicity was observed with hydrogen sulfide gas in Ames/salmonella assays using TA97, TA98, and TA100 strains, either with or without S9 liver fractions, of male Syrian golden hamsters or Sprague-Dawley rats that had been induced with 500 mg/kg Aroclor 1254,(EPA 1984). However, it should be noted that the concentration of hydrogen sulfide gas was limited by its solubility in ethanol, which was the test solvent (EPA 1984). The highest dose that could be obtained was 1,750 µg/plate.
Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

There was no increase in cancer incidence noted in a residential cohort study of individuals living downwind from natural gas refineries in Alberta, Canada, from 1970 to 1984 (Schecter et al. 1989). In a retrospective epidemiologic study using cancer registry data from 198l-1990, Bates et al. (1998) evaluated the risk of cancer to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but the authors indicate concerns that exposures to hydrogen sulfide and/or mercury from geothermal sources could have health impacts. In their previous work it was indicated that the most rehable monitoring information for hydrogen sulfide in the area came from a monitoring exercise in 1978 that found a median concentration of hydrogen sulfide of 20 µg/m^3, with 35% of the measurements over 70 µg/m^3 and 10% over 400 µg/m^3 (Bates et al, 1997). Based on the cancer registry information, these workers found a significantly increased risk of nasal cancers (standardized incidence ratio [SIR] = 3.17; p = 0.01) among Rotorua residents as compared to the rest of the population of New Zealand. However, since this is a rare cancer, this finding is based on only four cancers. Because the population of Rotorua has a higher percentage of Maoris than the rest of New Zealand, these researchers also examined their data stratified by ethnicity and sex and found a significantly increased risk of cancers of the trachea, bronchus, and lung (SIR = 1.48; p = 0.02) among female Maoris in Rotorua as compared to female Maoris in the rest of New Zealand. Differences in smoking history between these two populations was not sufficient to explain the observed differences in risk. The authors concluded that the lack of adequate exposure

information did not permit findings of causal relationships between hydrogen sulfide and cancer incidence, but that the elevated disease rates were consistent with what might be expected ". ..if sufficient exposures to hydrogen sulfide and/or mercury were occurring."

No studies were located regarding cancer effects in animals after inhalation exposure to hydrogen sulfide.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans or animals after oral exposure to hydrogen sulfide.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, dermal, or ocular effects after oral exposure to hydrogen sulfide.

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to hydrogen sulfide.

Diarrheic digestive disorder was observed in adult pigs fed hydrogen sulfide at a dose level of 1.5 mg/kg/day for a few days (Wetterau et al. 1964). The study authors reported that in a repeat study using younger pigs that weighed less, no diarrheic disorder was noted.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to hydrogen sulfide.

Decreased body weight gain (48.2 kg total weight gain in treated animals versus 62.5 kg total weight gain in controls) was observed in pigs fed hydrogen sulfide at a dose level of 6.7 mg/kg/day for 105 days (Wetterau et al. 1964).

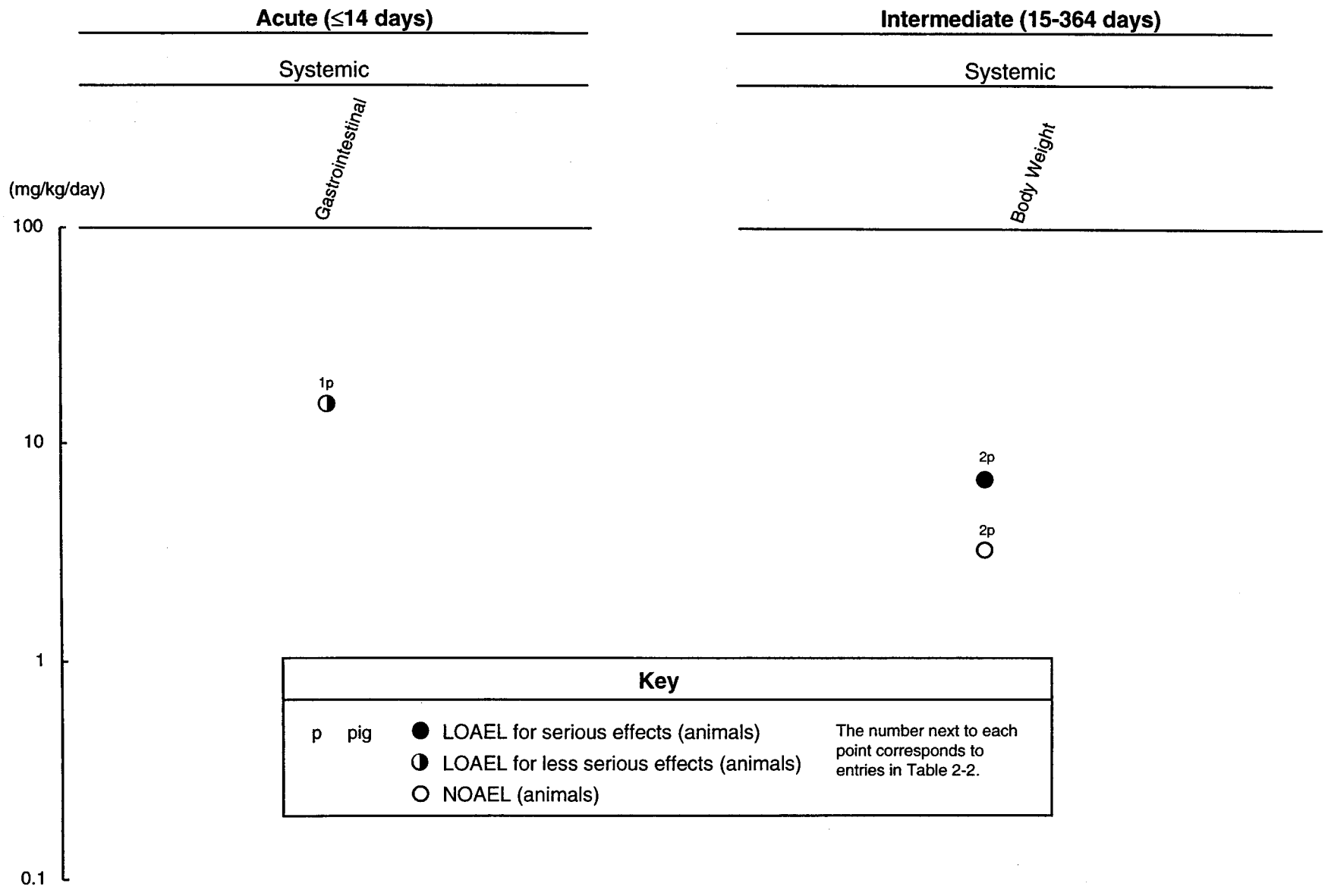
TABLE 2-2. Levels of Significant Exposure to Hydrogen Sulfide - Oral

Key to figure[a]	Species (Strain)	Exposure Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Systemic						
1	Pig (NS)	few d (F)	Gastro		15.0 (diarrheic digestive disturbance)		Wetterau et al. 1964
	INTERMEDIATE EXPOSURE						
	Systemic						
2	Pig (NS)	105 d (F)	Bd Wt	3.2		6.7 (23% decrease in body weight gain)	Wetterau et al. 1964

[a]The numbers correspond to entries in Figure 2-2.

Bd Wt = body weight; (F) = food; Gastro = gastrointestinal; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

Figure 2-2. Levels of Significant Exposure to Hydrogen Sulfide - Oral



No studies were located regarding the following health effects in humans or animals after oral exposure to hydrogen sulfide.

2.2.2.3 Immunological and Lymphoreticular Effects
2.2.2.4 Neurological Effects
2.2.2.5 Reproductive Effects
2.2.2.6 Developmental Effects
2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to hydrogen sulfide.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to hydrogen sulfide.

A study by Laug and Draize (1942) reported death in two out of three rabbits exposed to unknown concentrations of hydrogen sulfide through either clipped, intact, or abraded skin. One rabbit with intact skin exposed to hydrogen sulfide for 2 hours survived, while another died in this interval. The rabbit exposed to hydrogen sulfide through abraded skin also died (Laug and Draize 1942). When two guinea pigs were exposed to unknown concentrations of hydrogen sulfide gas for 60 minutes on a small area of their shaved abdomen, neither died (Walton and Witherspoon 1925). However, both guinea pigs that had their entire shaved torso (about 50% body area) exposed to an unknown concentration of hydrogen sulfide died after about 45 minutes (Walton and Witherspoon 1925). No clinical signs of toxicity were seen in a dog with shaved abdomen exposed full body (except head) to unknown concentrations of hydrogen sulfide in a chamber for 1 hour (Walton and Witherspoon 1925).

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, or ocular effects in humans or animals after dermal exposure to hydrogen sulfide. However, several sources indicate that care must be taken with liquefied hydrogen sulfide in order to avoid frostbite (ATSDR 1994; NIOSH 1997).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after dermal exposure to hydrogen sulfide.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to hydrogen sulfide. No clinical signs of neurotoxicity were seen in two guinea pigs exposed to an unknown concentration of hydrogen sulfide gas for 60 minutes on a small area of their shaved abdomen (Walton and Witherspoon 1925). A dog exposed to an unknown concentration of hydrogen sulfide for 1 hour showed no clinical signs of neurotoxicity (Walton and Witherspoon 1925).

No studies were located regarding the following health effects in humans or animals after dermal exposure to hydrogen sulfide:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to hydrogen sulfide.

2.3 TOXICOKINETICS

Although hydrogen sulfide is primarily absorbed through the lungs, it can also be absorbed through the gastrointestinal tract and intact skin (Laug and Draize 1942; Wetterau et al. 1964). It is metabolized through three pathways: oxidation, methylation, and reactions with metalloproteins or disulfide-containing proteins (Beauchamp et al. 1984). Although the major metabolic pathway for detoxification of hydrogen sulfide is oxidation in the liver, the methylation pathway also serves as a detoxification route (EPA 1987a; Weisiger and Jakoby 1980). The major oxidation product of sulfide is thiosulfate, which is then believed to be converted to sulfate and subsequently excreted in urine (Bartholomew et al. 1980). The toxicity of hydrogen sulfide is a result of reactions with metalloproteins (Smith and Gosselin 1979) found in many enzymes. In the mitochondria, cytochrome oxidase, the final enzyme in the respiratory chain, is inhibited by hydrogen sulfide as a result of the oxygen reduction of one of the enzymatic hemes (Chance and Schoener 1965; EPA 1987a; Nicholls 1975; Nicholls et al. 1976; Petersen 1977; Smith and Gosselin 1979; Smith et al. 1977; Wever et al. 1975). Inhibition of cytochrome oxidase prevents oxygen from acting as the final electron acceptor and causes blockage of oxidative metabolism by inhibiting the electron transport chain.

Hydrogen sulfide is widely distributed in the body. Sulfides have been found in the liver, blood, brain, lungs, spleen, and kidneys of humans who died after accidental inhalation exposure.

Hydrogen sulfide is excreted primarily as sulfate (free sulfate or thiosulfate) in the urine. It is also excreted unchanged in exhaled air and in feces and flatus.

2.3.1 Absorption

2.3.1 .I inhalation Exposure

Hydrogen sulfide is absorbed rapidly through the lungs (Adelson and Sunshine 1966; Allyn 1931; Breysse 1961; Deng and Chang 1987; Hagley and South 1983; Kimura et al. 1994; NIOSH 1991; Osbern and Crapo 1981; Parra et al. 1991). Inhalation absorption of lethal concentrations of hydrogen sulfide is rapid in

humans, and effects can occur within seconds to minutes. Inhalation is the most common route of hydrogen sulfide exposure. Hydrogen sulfide dissociates at physiological pH to the hydrogen sulfide anion, which is probably the absorbed form (WHO 1987). No quantitative data are available regarding the absorption of hydrogen sulfide in humans.

Animal data, while demonstrating that absorption of hydrogen sulfide via the lungs occurs readily and rapidly, are not sufficient to quantitatively determine the proportion of an inhaled dose that is absorbed (Beck et al. 1979; Kage et al. 1992; Khan et al. 1990; Lopez et al. 1989; Nagata et al. 1990; Prior et al. 1988, 1990; Smith and Gosselin 1964; Tansy et al. 1981). No physiologically based pharmacokinetic (PBPK) models have been developed to provide estimates of hydrogen sulfide absorption.

2.3.1.2 Oral Exposure

Hydrogen sulfide exists as a gas; therefore, oral exposure to hydrogen sulfide will not normally occur. No studies were located regarding absorption in humans after oral exposure to hydrogen sulfide. Some case reports showing accidental oral ingestion of liquid manure or other substances that might contain hydrogen sulfide exist, but in all of these cases, the ingestion was secondary to being "knocked down" by inhalation of hydrogen sulfide (Freireich 1946; Imamura et al. 1996; Kimura et al. 1994; Osbern and Crapo 198 1).

One animal study suggests that hydrogen sulfide can be absorbed through the gastrointestinal tract. A study where pigs were fed diets containing dried greens with levels of hydrogen sulfide of 1.5, 3.1, or 6.7 mg/kg/day for 105 days indicated that hydrogen sulfide is absorbed following ingestion (Wetterau et al. 1964).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal hydrogen sulfide exposure.

Animal data have shown that dermal hydrogen sulfide absorption can occur, although large surface areas of skin must be exposed. Trunk fur of rabbits was clipped for exposure to unknown concentrations of hydrogen sulfide gas for 1.5-2 hours; evidence for the absorption of hydrogen sulfide included both the death of the animals and a positive sulfide reaction of expired air with lead acetate paper (Laug and Draize 1942). No evidence of dermal absorption was found in two guinea pigs exposed to unknown concentrations of hydrogen

sulfide gas for 1 hour on a small area of their shaved abdomens (Walton and Witherspoon 1925). Dermal absorption was indicated, however, when the entire torso of guinea pigs was exposed to hydrogen sulfide gas and the animals died after about 45 minutes (Walton and Witherspoon 1925). No clinical signs of toxicity were reported in a dog that received full-body exposure (except head) to unknown concentrations of hydrogen sulfide (Walton and Witherspoon 1925).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Few human data are available regarding tissue distribution after inhalation exposure to hydrogen sulfide. One case study reported sulfide (as bis[pentafluourobenzyl]sulfide) distribution in three of four men who drowned after being overcome, presumably, by hydrogen sulfide and falling unconscious into a lake in Japan (Kimura et al. 1994). Concentrations of hydrogen sulfide gas were estimated to be 550-650 ppm, based upon extrapolation of tissue concentrations from rat studies (Kimura et al. 1994; Nagata et al. 1990). Initial blood sulfide concentrations determined 2-3 hours postmortem in these individuals were 0.1,0.2, and 0.08 µg/g tissue, while at 24 hours after death the levels were 0.5 µg/g, 0.23 µg/g, and undetected, respectively. At 24 hours after death, sulfide concentrations in the brains of these individuals were 0.2, 0.4, and 1.06 µg/g, and lung concentrations were 0.68,0.21 s and 0.23 µg/g. Based on a study in rats by this same group of researchers (Nagata et al. 1990) that showed little or no increase in sulfide concentrations in rat lung and brain 24 hours after death, as well as a lack of sulfide in these tissues in control rats, Kimura et al. postulated that the sulfide levels observed in the brain and lungs in the human study may be indicators of tissue levels at the time of death (Kimura et al. 1994). Sulfide was detected in liver (1.30-l .56 µg/g), spleen (0.32-0.64 µg/g), and kidney (0.47-l .50 µg/g) (Kimura et al. 1994). Hydrogen sulfide levels of 0.92 µg/g in blood, 1.06 µg/g in brain, 0.34 µg/g in kidney, and 0.38 µg/g in liver were detected at autopsy in a man who was overcome by hydrogen sulfide in a tank (Winek et al. 1968). Hydrogen sulfide concentrations in the tank after the accident were 1,900-6,100 ppm (Winek et al. 1968).

Data from animal studies suggest that the distribution of inhaled hydrogen sulfide is rapid and widespread, while storage of hydrogen sulfide in the body is limited by rapid metabolism and excretion. Adult male rats exposed to 550 or 650 ppm hydrogen sulfide until death had tissue samples taken at 0,4,24, and 48 hours after death (Nagata et al. 1990). Sulfide concentrations were measured 1, 7, and 30 days later. Immediately after death, sulfide concentrations in whole blood were 0.48 µg/g in exposed animals and were nondetectable

in control animals. Sulfide concentrations rapidly increased with time after death in both control and treated animals. Significant increases in sulfide concentrations were found in the lung (0.60 µg/g), brain (0.31 µg/g), thigh muscle (0.21 µg/g), and abdominal muscles (0.22 µg/g), as compared to controls (tissues collected immediately after death) (Nagata et al. 1990). Liver and kidney samples had similar sulfide concentrations in both exposed and control groups when taken immediately after death. Certain tissues (blood, liver, and kidneys) exhibited an increase in sulfide concentration with time after death, whether hydrogen sulfide exposure occurred or not, while other tissues (lung, brain, and muscle) had little or no change in sulfide concentration (Nagata et al. 1990).

Distribution of hydrogen sulfide in male Wistar rats was examined by Kohno et al. (1991). Animals exposed to 75 ppm hydrogen sulfide for 20,40, or 60 minutes showed essentially the same distribution of hydrogen sulfide irrespective of duration: 10 µg/mL blood, 25 µg/g brain, 20 µg/g lung, 37 µg/g heart, 20 µg/g liver, 25 µg/g spleen, and 30 µg/g kidney. Thus, the organ with the highest concentration of hydrogen sulfide in this study was the heart.

Japanese white rabbits exposed to 500-l, 000 ppm of hydrogen sulfide (the lethal concentration), for 60 minutes, had thiosulfate concentrations of 0.08 µmol/mL in blood, 0.095 µmol/g in lung, and 0.023 µmol/g in brain (Kage et al. 1992). Little or no thiosulfate was found in the liver, kidney, or muscle. When rabbits were exposed to 100-200 ppm of hydrogen sulfide for 60 minutes, blood thiosulfate levels decreased from 0.061 umol/mL immediately postexposure to a trace level at 2 hours postexposure (Kage et al. 1992).

2.3.2.2 Oral Exposure

No studies were located regarding tissue distribution in humans or animals after oral exposure to hydrogen sulfide.

2.3.2.3 Dermal Exposure

No studies were located regarding tissue distribution in humans or animals after dermal exposure to hydrogen sulfide.

2.3.2.4 Other Routes of Exposure

No studies were located regarding tissue distribution in humans or animals after hydrogen sulfide exposure by other routes.

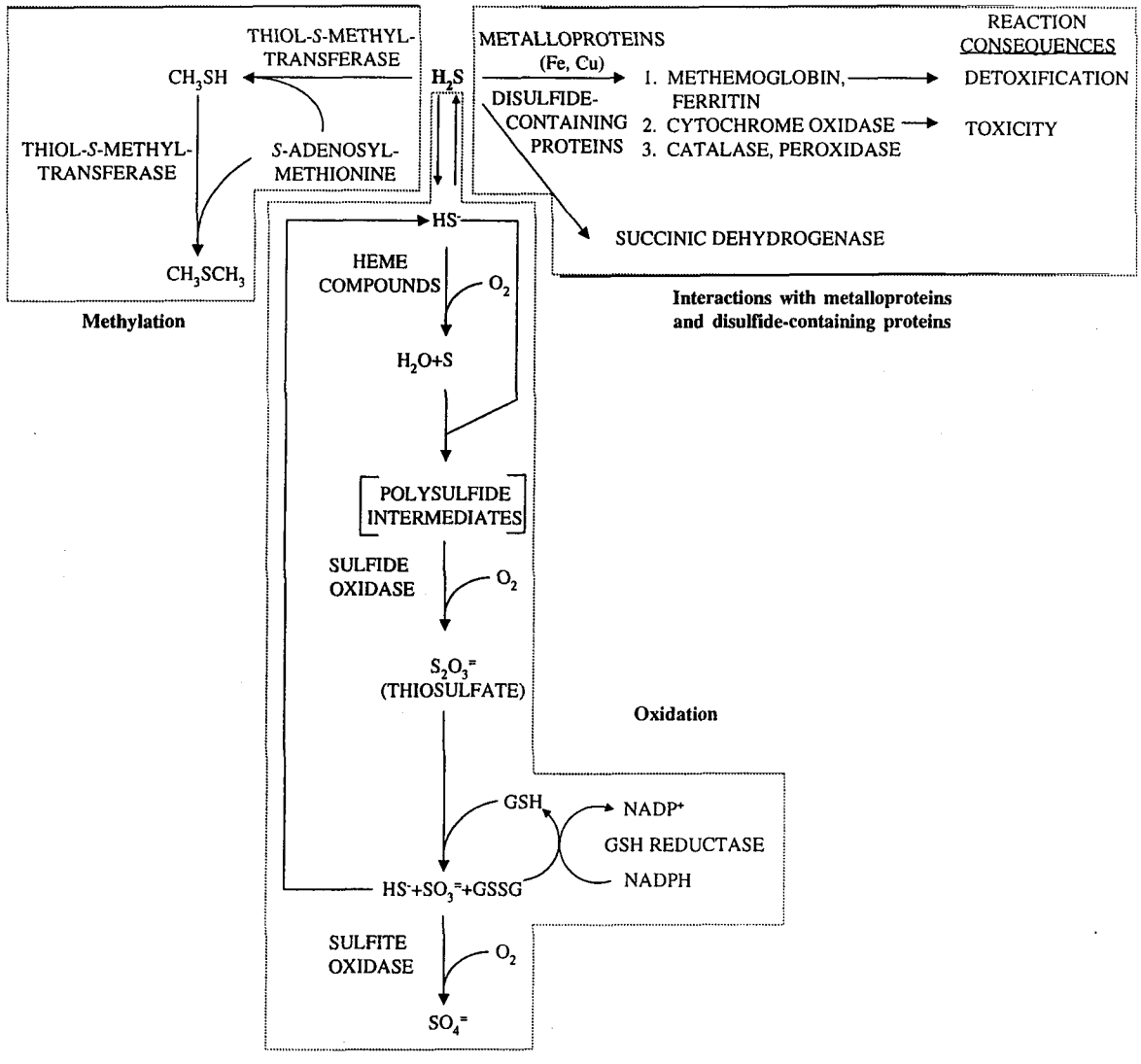
2.3.3 Metabolism

Hydrogen sulfide metabolism occurs through three pathways: oxidation, methylation, and reaction with metallo- or disulfide-containing protein (Beauchamp et al. 1984; EPA 1987a). Hydrogen sulfide is primarily detoxified by oxidation reactions to sulfate (Tabacova 1986). Hydrogen sulfide can also be detoxified by methylation (EPA 1987a; Weisiger and Jakoby 1980). The toxicity of hydrogen sulfide results from its reactions with cytochrome oxidase (Beauchamp et al. 1984; EPA 1987a; Smith and Gosselin 1979). The proposed detoxification pathways most currently accepted for the metabolism of hydrogen sulfide are shown in Figure 2-3 and include oxidation and methylation, as well as the toxic pathways resulting from interactions with metalloproteins and disulfide-containing proteins.

The major metabolic pathway for hydrogen sulfide in the body is the oxidation of sulfide to sulfate, which is excreted in the urine (Beauchamp et al. 1984). The major oxidation product of sulfide is thiosulfate, which is then converted to sulfate; the primary location for these reactions is in the liver (Bartholomew et al. 1980).

Urinary thiosulfate levels were measured in volunteers exposed to 8, 18, or 30 ppm of hydrogen sulfide for 30-45 minutes and compared to levels in unexposed individuals at a pelt processing plant (Kangas and Savolainen 1987). Very little urinary thiosulfate was excreted in controls (2.9 pmolImmo1 creatinine). The highest urinary thiosulfate levels among exposed individuals occurred 15 hours after exposure and decreased to control levels by 17 hours postexposure (Kangas and Savolainen 1987). Most absorbed hydrogen sulfide was already oxidized by 15 hours postexposure (Kangas and Savolainen 1987). This study was limited by the lack of summary data on exposed individuals and inadequate data regarding the numbers of subjects. Using perfused rat liver, Bartholomew et al. (1980) found that there was a rapid oxidation of ^{35}S-sulfide to sulfate. Furthermore, there was a decrease in thiosulfate released from the liver when nonlabelled thiosulfate was added to the perfusion system, suggesting that thiosulfate may act as an intermediate in the oxidation to sulfate (Bartholomew et al. 1980).

FIGURE 2-3. Metabolic Pathways of Hydrogen Sulfide*



*Adapted from Beauchamp et al. 1984

2. HEALTH EFFECTS

Japanese white rabbits exposed to 500-1,000 ppm hydrogen sulfide (the lethal concentration, for 14-30 minutes) had thiosulfate concentrations of 0.08 µM/mL in blood, 0.095 µM/g in lung, and 0.023 µM/g in brain (Kage et al. 1992). Although sulfide was not detected in blood or urine samples of rabbits exposed to a concentration of 100-200 ppm hydrogen sulfide for 60 minutes, thiosulfate levels were highest (1.2 µM/mL) 1-2 hours after exposure and could still be detected in urine 24 hours after exposure (Kage et al. 1992). Thiosulfate levels in blood peaked (0.061 µM/mL) immediately after exposure and were undetectable after 4 hours (Kage et al. 1992).

Evidence for the methylation of hydrogen sulfide comes primarily from *in vitro* studies of Sprague-Dawley rats' intestinal mucosa (Weisiger et al. 1980). Thiol S-methyltransferase catalyzed the methylation of hydrogen sulfide to methanethiol (CH_3SH). Methanethiol can act as a substrate for another methylation also catalyzed by thiol *S*-methyltransferase, yielding dimethylsulfide (CH_3SCH_3,). The activity of thiol *S*-methyltransferase was widely distributed, with the greatest in cecal and colonic mucosa, liver, lung, and kidney, and was also found in other parts of the intestine and stomach, spleen, heart, and skeletal muscle. No enzyme activity was found in the feces. Although it has been postulated that methylation is a method of detoxification of hydrogen sulfide, a constituent of human flatus produced in the intestine, the extent to which the toxicity of exogenous hydrogen sulfide is attenuated by methylation is not known.

The interaction of hydrogen sulfide with metalloproteins was postulated because the mechanism of toxicity for hydrogen sulfide is the inhibition of cytochrome oxidase and thus, inhibition of the electron transport system. It appears that hydrogen sulfide interacts with other metalloproteins and may represent a detoxification pathway in some instances (Beauchamp et al. 1984). Reduction of disulfide bridges by hydrogen sulfide was suggested by Smith and Abbanat (1966) who found that mice were protected from lethal concentrations of hydrogen sulfide by the administration of oxidized glutathione. This protection was not afforded by the administration of reduced glutathione. The study authors believed that the disulfide linkage of the oxidized glutathione interacted with the hydrosulfide, which prevented the reaction of sulfide with other sites (Smith and Abbanat 1966). This is attributed to the polarizability of the disulfide bond. The nucleophilic sulfhydryl group of hydrogen sulfide reacts with the 6' of the disulfide bond, thus converting it to a less toxic product.

No studies were located regarding metabolism in humans or animals after oral, dermal, or other routes of exposure to hydrogen sulfide.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

The major metabolic pathway for hydrogen sulfide in the body is oxidation of sulfide to sulfate, with the sulfate being excreted in the urine (Beauchamp et al. 1984). Thiosulfate excretion was measured in volunteers exposed to 8, 18, or 30 ppm of hydrogen sulfide for 30-45 minutes and compared to that of unexposed individuals at a pelt processing plant (Kangas and Savolainen 1987). The study did not report the summary results of all exposed individuals; however, data from 1 individual exposed to 18 μpm hydrogen sulfide for 30 minutes found urinary thiosulfate concentrations of approximately 2,4,7, 30, and 5 μM/mM creatinine at 1, 2,5, 15, and 17 hours postexposure, respectively. The highest urinary thiosulfate levels among exposed individuals occurred 15 hours after exposure and dropped to control levels by 17 hours postexposure.

Kage et al. (1992) evaluated sulfide and thiosulfate levels in the blood and urine of Japanese white rabbits exposed to 100-200 ppm for 60 minutes and concluded that thiosulfate was a better marker for exposure since it could be detected immediately in the blood but also was detectable in the urine 24 hours after exposure. In the blood, thiosulfate levels decreased from 0.061 μM/mL immediately following exposure to an undetectable amount after 4 hours (Kage et al. 1992). In urine samples from these same animals, thiosulfate levels were highest (1.2 μM/mL) l-2 hours after exposure but were still detectable after 24 hours of exposure at slightly higher level than that of control (Kage et al. 1992).

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans or animals after oral exposure to hydrogen sulfide.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to hydrogen sulfide.

Excretion of hydrogen sulfide was documented after dermal exposure in rabbits. Trunk fur of rabbits was clipped and left intact or abraded for exposure to hydrogen sulfide gas (unknown concentrations) for 1.5-2 hours; the animals then breathed clean air (Laug and Draize 1942). Evidence for the excretion of

hydrogen sulfide by the rabbits was a sulfide reaction of the expired air with lead acetate paper (Laug and Draize 1942). Sulfides in the expired air were noted in one rabbit with intact skin after 7 minutes of exposure. This study was limited by the lack of measurement of exposure concentrations and the small number of animals used.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following *various* combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose, Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

If PBPK models for hydrogen sulfide exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

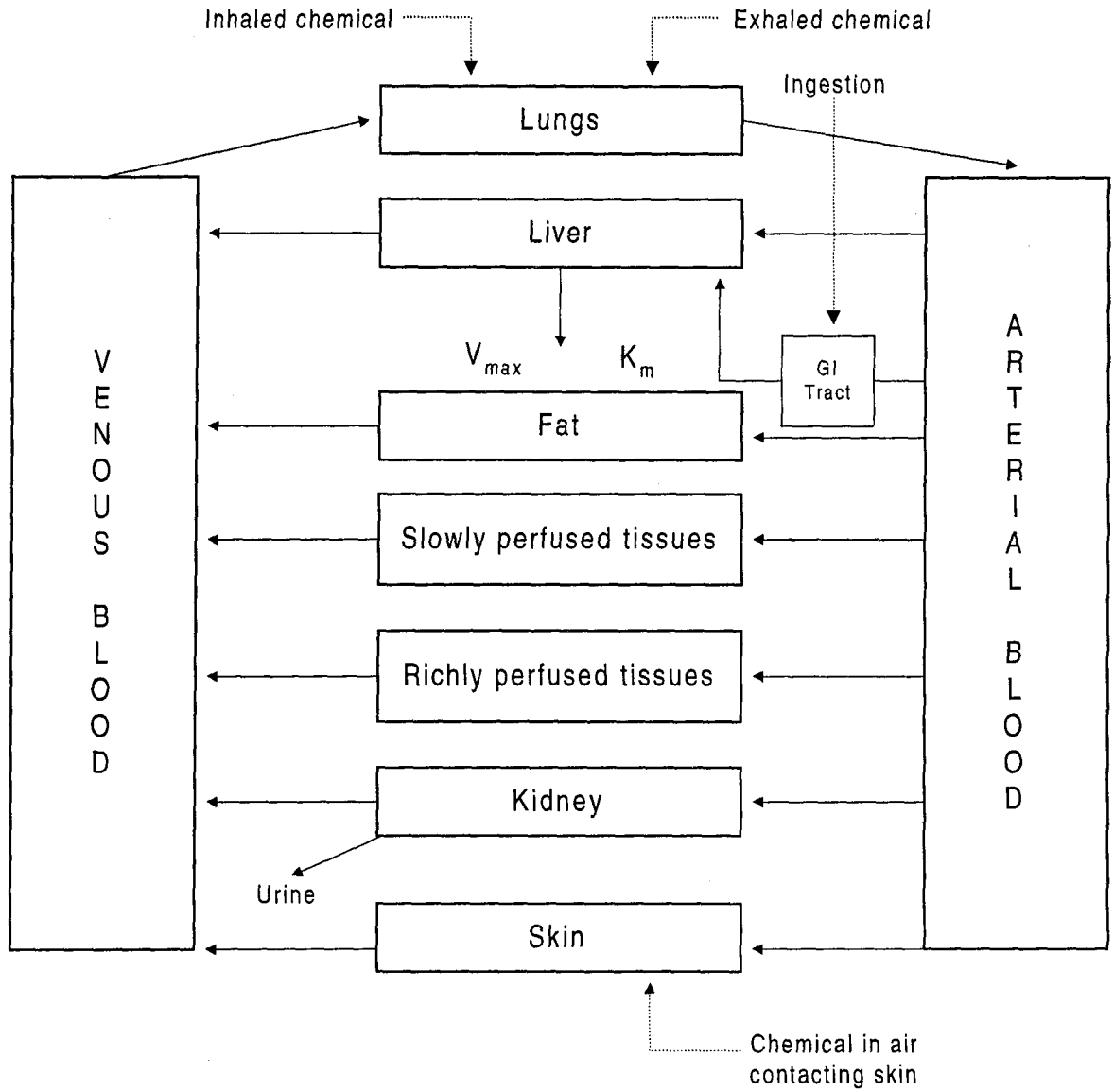
There are no PBPK models for hydrogen sulfide.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Hydrogen sulfide is primarily absorbed through the lungs. It can also be absorbed through the gastrointestinal tract and the skin. Hydrogen sulfide is widely distributed in the body after inhalation exposure. Based on analyses of tissues from humans who died after accidental exposure, sulfides have been detected in the liver, blood, brain, lungs, spleen, and kidneys. Hydrogen sulfide is metabolized by oxidation, methylation, and reaction with metalloproteins or disulfide-containing proteins. The major metabolic pathway for detoxification of hydrogen sulfide is oxidation of the sulfide to sulfate in the liver. Hydrogen sulfide is excreted primarily as sulfate in the urine.

Figure 2-4. Conceptual Representation of a Physiologically-Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically-based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

2.4.2 Mechanisms of Toxicity

Exposure to hydrogen sulfide causes an initial increase in the rate of respiration as a result of the stimulation of the carotid bodies, chemosensors associated with ventilatory control (Ammann 1986; Hagley and South 1983). Under normal conditions, these chemosensors stimulate ventilation of the lung during extreme cases in which a significant decrease in the partial pressure of oxygen in the arterial blood traveling to the head occurs (Ammann 1986). This action results in an increase in the number of impulses originating from the chemosensors to the respiratory center in the brain. The rate and depth of ventilation increases to the point of hyperpnea (rapid, deep breathing).

Direct inhibition of cellular enzymes has been postulated as one of many underlying mechanisms of toxicity of hydrogen sulfide (Beauchamp et al. 1984; Deng 1992). In particular, cytochrome oxidase, an enzyme involved in cellular oxidative processes and energy production, has been implicated. Inhibition of cytochrome oxidase is believed to disrupt the electron transport chain and to significantly impair oxidative metabolism, leading to anaerobic metabolism, severely decreased ATP production with curtailed cellular energy generation, and the generation of lactic acid. Nervous and cardiac tissues, which have the highest oxygen demand, are especially sensitive to the disruption of oxidative metabolism (Ammann 1986). In the central nervous system, this effect may result in death from respiratory arrest. Inhibition of cytochrome oxidase by hydrogen sulfide is similar to that of cyanide (Smith and Gosselin 1979). However, the mechanism by which hydrogen sulfide inhibits cytochrome oxidase differs from that of cyanide (NIOSH 1977b).

Although the suggestion has been frequently made that the effects of hydrogen sulfide on nervous tissue are, as with cyanide, simply due to inhibition of oxidative metabolism, recent authors suggest that this is not the case. Reiffenstein et al. (1992) examined this issue and concluded that while treatment with hydrogen sulfide and anoxic conditions arrive at the same end point, there are pharmacological dissimilarities. Baldelli et al. (1993) investigated the mechanism of toxicity associated with hydrogen sulfide exposure (achieved by intravenous injection of sodium sulfate) and concluded that it resulted not from a direct toxicity on central nervous system neurons, i.e., a ‘cerebral necrosis’ resulting from poisoning of mitochondria respiration, but rather, from an indirect effect associated with a profound hypotension most likely due to cardiotoxicity. These authors emphasized the importance of immediate cardiopulmonary resuscitation as a way to prevent the delayed toxicity associated with hydrogen sulfide “knock-down” exposures.

2. HEALTH EFFECTS

An electrophysiological study of the effects of hydrogen sulfide on membrane and synaptic properties of dorsal raphe serotonergic cells in an in vitro rat brain-stem slice preparation has elucidated a possible mechanism of neurotoxicity of hydrogen sulfide (Kombian et al. 1993). These neurons are considered to play an important role in central nervous system control of respiratory rhythm. Hydrogen sulfide has been shown to produce two reversible, concentration-dependent effects on the resting membrane properties of the dorsal raphe neurons. Some neurons (14%) responded to hydrogen sulfide with an outward current accompanied by an increase in conductance, while 39% of the neurons responded with a rapid-onset depolarization corresponding to a weakly voltage-dependent inward current showing little or no change in conductance. In addition, 30% of the neurons displayed both types of responses. Finally, 18% of the neurons were unresponsive to hydrogen sulfide. The outward current induced by hydrogen sulfide was demonstrated to be caused by an elevated conductance to potassium, whereas the hydrogen sulfide-induced inward current is carried by calcium ions. However, the mechanism of calcium ion entry is not clear.

Hydrogen sulfide was shown to inhibit, in a concentration-dependent fashion, all components of the complex evoked synaptic responses of the dorsal raphe serotonergic neurons (Kombian et al. 1993). This effect was rapid and reversible, and involved both pre- and postsynaptic mechanisms. Similar effects of hydrogen sulfide on brain hippocampal CA1 neurons have been reported. The electrophysiological effects of hydrogen sulfide are comparable to those elicited by anoxia. The neuronal action of hydrogen sulfide may involve an interaction with free thiols and disulfide bonds present in most membrane proteins. Collectively, the electrophysiology data suggest a possible role of the effects of hydrogen sulfide on synaptic and membrane properties of the dorsal raphe serotonergic neurons of the brain stem in the cessation of respiratory drive following acute hydrogen sulfide exposure.

Inhibition of monoamine oxidase has been proposed as a possible mechanism underlying the hydrogen sulfide-mediated disruption of neurotransmission in brain stem nuclei controlling respiration (Warenycia et al. 1989a). Administration of sodium hydrosulfide, an alkali salt of hydrogen sulfide, has been shown to increase brain catecholamine and serotonin levels in rats. It has also been suggested that persulfide formation resulting from sulfide interaction with tissue cystine and cystinyl peptides may underlie some aspects of hydrogen sulfide neurotoxicity, including inhibition of monoamine oxidase (Warenycia et al. 1990).

2.4.3 Animal-to-Human Extrapolations

The toxicokinetic disposition of hydrogen sulfide in humans is not understood. However, available toxicity and toxicokinetic data indicate that hydrogen sulfide can be readily absorbed through the lung and, to a lesser and clinically irrelevant extent, through the gastrointestinal tract and skin. Although the metabolism of hydrogen sulfide has been characterized in animals, there are limited data to suggest that the metabolism of hydrogen sulfide may be in part similar in humans. For instance, human data indicate that hydrogen sulfide is oxidized to sulfate and thiosulfate and excreted in the urine. Neurotoxicity induced by hydrogen sulfide has been observed in experimental animals and humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Issues relevant to children are explicitly discussed in 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Overview

Humans may be exposed to hydrogen sulfide both from its endogenous production or from exogenous sources. Most endogenous production apparently results from the metabolism of sulfhydryl-containing amino acids, e.g., cysteine, by bacteria present in both the intestinal tract and the mouth (Beauchamp et al. 1994; Tonzetich and Carpenter 1971); however, it is also produced in the brain and several smooth muscles, e.g., thoraic aorta, by enzymes found in these tissues (Abe and Kimura 1996; Hosoki et al. 1997). Hydrogen sulfide produced in the gut may be detoxified or excreted in feces or flatus. In flatus, hydrogen sulfide concentrations as high as 18 ppm were recorded by Kirk (1949) in individuals on a normal diet. In these experiments, between 40 and 90% of normal individuals produced hydrogen sulfide; mean values over a 4 year period were between 1 and 4 ppm. Hydrogen sulfide produced in the mouth is one of the sulfur compounds contributing to halitosis; hydrogen sulfide in mouth air has been measured at levels between 1 and 100 ppb (Rosenberg et al. 1991). In at least one disease state (ulcerative colitis) sulfide produced in the colon appears to play a role in pathogenesis (Roediger et al. 1997). It is not clear whether this is because affected individuals produce more hydrogen sulfide or detoxify it less effectively; however, Moore et al. (1997) did not observe elevated levels of colonic luminal hydrogen sulfide in patients with ulcerative colitis. Guidotti (1994) has noted that the ability to detoxify organosulfides is deficient in 10% or more of the

population and suggests that this trait might be a marker for persons susceptible to hydrogen sulfide-induced toxicity at levels lower than those at which the rest of the population responds.

Hydrogen sulfide is also produced endogenously in the brain; in rats the endogenous concentration was around 1.6 ppm (Warenycia et al. 1989a). Investigation into the role of hydrogen sulfide in the brain found that physiological concentrations selectively enhanced certain receptor-mediated responses and facilitated the induction of hippocampal long-term potentiation, which lead the authors to suggest that hydrogen sulfide functions as a neuromodulator in the brain, possibly playing a role in associative learning (Abe and Kimura 1996). However, in rats, the lethal concentration in brain was just double the endogenous concentration suggesting that the margin of safety between physiologic function and toxicity may be fairly narrow. Similarly, the production of hydrogen sulfide by the ileum, portal vein, and thoracic aorta has recently been described (Hosoki et al. 1997). These authors found that while exogenously applied hydrogen sulfide relaxed these smooth muscles, much lower concentrations of hydrogen sulfide enhanced the smooth muscle relaxation induced by nitric oxide (NO) in the thoracic aorta. Thus, these authors suggest that endogenous hydrogen sulfide may regulate smooth muscle tone in synergy with NO.

The inhalation route is the major route of exogenous exposure to hydrogen sulfide. Most human data are derived from case reports and occupational studies although there is also limited information from community studies. Hydrogen sulfide tends to be a problem in communities located near certain types of industrial sites, including pulp and paper mills, gas refineries, or geothermal power plants, although these sites can often also release other irritants, such as sulfur dioxide. Landfills are also a common source of ambient hydrogen sulfide. Although they may only be exposed to low levels of hydrogen sulfide, people living in communities surrounding these sites typically complain of symptoms such as eye irritation, respiratory problems, and headache. The principal adverse health effects noted in humans acutely exposed to high concentrations of hydrogen sulfide by inhalation include neurologic and respiratory effects; death may result as a consequence of respiratory failure. Hydrogen sulfide is also an ocular and respiratory tract irritant. These effects can occur at much lower concentrations than those that cause severe effects. There is also some evidence that exposure to hydrogen sulfide may be associated with an increased rate of spontaneous abortion; however, this needs confirmation in a well-designed epidemiologic study with well-characterized exposures. Insufficient data exist to determine whether hydrogen sulfide is carcinogenic, although available data suggest that it is not.

2. HEALTH EFFECTS

Effects observed in animals are similar to those that have been observed in humans. Death has occurred in animals after inhalation of high concentrations of hydrogen sulfide. Acute inhalation exposures to hydrogen sulfide have also resulted in respiratory, cardiovascular, neurological, hepatic, body weight, and developmental effects in animals. Gastrointestinal effects have been noted in animals after oral exposure to hydrogen sulfide.

The mechanism of hydrogen sulfide toxicity is in part similar to that of cyanide. Like cyanide, hydrogen sulfide can inhibit the enzyme cytochrome oxidase resulting in tissue hypoxia. Specific health effects are discussed in greater detail below,

Minimal Risk Levels for Hydrogen Sulfide

Inhalation MRLS

- An MRL of 0.07 ppm has been derived for acute-duration inhalation exposure to hydrogen sulfide. This MRL is based on a LOAEL of 2 ppm for respiratory effects-bronchial obstruction (30% change in airway resistance) in 2/10 persons with asthma reported in the Jappinen et al. 1990 study (Table 2-1 LSE #16). An uncertainty factor of 30 was applied, 10 for the use of a LOAEL, and 3 for human variability. Since persons with severe asthma were excluded from the study, an uncertainty factor of 3 is needed to protect all sensitive individuals including children. Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

- An MRL of 0.03 ppm has been derived for intermediate-duration inhalation exposure to hydrogen sulfide. This MRL is based on a NOAEL of 30.5 ppm for respiratory effects in mice based on the CRT 1983a study (Table 2-l LSE #39). The NOAEL is adjusted for intermittent exposure and the $NOAEL_{[HEC]}$, is calculated. An uncertainty factor of 30 is then applied, 3 for extrapolating from animals to humans and 10 for human variability. Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

A chronic-duration inhalation MRL was not derived since data were insufficient.

Oral MRLS

No oral MRLs were derived since data were insufficient.

Death. At high concentrations (>500 ppm), inhalation of hydrogen sulfide can result in rapid unconsciousness and death due to respiratory arrest after only a few breaths. Numerous case reports of human deaths following acute inhalation exposure to hydrogen sulfide have been published (Allyn 193 1; Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Freireich 1946; Hagley and South 1983; Morse et al. 1981); in the period between 1983-I 99229 deaths due to hydrogen sulfide were reported to poison control centers (Snyder et al. 1995). Symptoms that may precede death include nausea, vomiting, dizziness, dyspnea, central nervous system depression, coma, seizures, and noncardiogenic pulmonary edema (Hoidal et al. 1986; Parra et al. 1991). One study comparing death rates between the general population and a population chronically exposed to low levels of hydrogen sulfide (1 O-400 ppb) found some evidence of an increased risk of dying from respiratory disease; however, the study suffered from a number of methodological flaws leading the authors (Bates et al. 1997) to conclude that the evidence was not compelling, though it probably warranted a more thorough examination.

Acute lethal concentrations (LC_{50}s) for hydrogen sulfide in rats have been reported to range from 335 to 587 ppm (Prior et al. 1988; Tansy et al. 1981) There are no reports of fatalities in humans or animals exposed solely by the oral route or dermal routes.

Systemic Effects

Respiratory Effects. In most case reports of acute accidental exposure to hydrogen sulfide and occupational studies, exposure concentrations and duration were not reported. However, acute inhalation exposure to >500 ppm hydrogen sulfide is considered to result in respiratory failure. Death is often the result of respiratory depression as a result of the action of hydrogen sulfide on the respiratory center in the brain. Respiratory distress was reported in 2 workers exposed to >40 ppm hydrogen sulfide for <25 minutes (Spolyar 1951). Other respiratory effects of hydrogen sulfide may include noncardiogenic pulmonary edema, cough, and dyspnea (Arnold et al. 1985; Krekel 1964). Hydrogen sulfide is a respiratory tract irritant, and exposure to >20 ppm can cause irritation of the mucous membranes (Ahlborg 1951). Cyanosis has been reported in a number of case reports involving accidental exposure to high airborne concentrations of

hydrogen sulfide and is believed to be the result of respiratory distress (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Peters 1981; Ravizza et al. 1982; Stine et al. 1976; Tvedt et al. 1991a, 1991b).

No changes in pulmonary function tests were observed in healthy volunteers exposed to 5 ppm hydrogen sulfide during either more than 16 minutes (Bhambhani and Singh 1991), or 30 minutes of exercise (Bhambhani et al. 1994), or in workers exposed to l-l 1 ppm of hydrogen sulfide (Jappinen et al. 1990). In addition, there was no significant alteration in pulmonary function in individuals exposed to 10 ppm hydrogen sulfide for 1.5 minutes during exercise compared to their control values (Bhambhani et al. 1996). However, 2 of 10 asthmatics had changes in a few parameters of pulmonary function following exposure to 2 ppm of hydrogen sulfide for 30 minutes, although the group as a whole had no significant changes in these parameters (Jappinen et al. 1990).

In a series of reports characterizing the subchronic and chronic effects on respiratory health of communities exposed to 'malodorous sulfur compounds' such as hydrogen sulfide, methyl mercaptan, and methyl sulfides from pulp mills, a group of researchers from Finland reported a significant increase in the reporting of nasal symptoms and cough in the previous 4 weeks and the previous year for populations living in two polluted communities as compared to a third, nonexposed community. The incidence of breathlessness or wheezing also increased but not to the level of significance. All three symptoms showed a dose-related increase across the three communities (Jaakkola et al. 1990). Measurements of the mean and maximum 4-hour concentrations of hydrogen sulfide levels in the most heavily-exposed community indicated levels of 4 and 56 $\mu g/m^3$ (2.8 and 39 ppb), respectively, while in the less heavily-exposed community these values were 2 and $\mu g/m^3$, (1.4 and 15.4 ppb), respectively. A subsequent study (Marttila et al. 1994b) of children in these same communities showed a similar increase in nasal symptoms and cough in children from the more heavily-exposed community, but none of these risks reached statistical significance. It should be noted, however, that the more heavily-exposed community also had higher mean and maximum levels of particulates and sulfur dioxide than the less-exposed community, thus making it difficult to attribute the effects observed solely to hydrogen sulfide.

This same group also evaluated the acute health effects associated with episodes of high emissions (Haahtela et al. 1992; Marttila et al. 1995). In the first study, increased emissions from a pulp mill resulted in increased concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 $\mu g/m^3$ and the 24-hour averages for the 2 days were 35 and 43 $\mu g/m^3$. Following the high exposure, and then later after a low exposure period (hydrogen sulfide level of 0.1 to 3.5 $\mu g/m^3$ for 4 hours), community

responses were evaluated with a questionnaire. Significant increases were observed in the prevalence of eye symptoms, breathlessness, nausea, headache, and mental symptoms between the two time periods. In this comparison the concentration of sulfur dioxide was the same (3 $\mu g/m^3$). In the later study, Marttila et al. (1995) compared community responses using six consecutive questionnaires after three predefined levels of exposure. The three exposure levels were expressed as $\mu g/m^3$ of total reduced sulfur (TRS) which this group had moved to as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <10 $\mu g/m^3$), medium (10-30 $\mu g/m^3$), and high exposure (>30 $\mu g/m^3$). The study found a dose-related increase in the probability of both nasal and pharyngeal symptoms. For nasal symptoms the probability ratios were 3.13 (95% CI 1.25 to 7.25) and 8.50 (95% CI 3.19 to 18.64) for medium and high exposure, respectively. For pharyngeal symptoms the probability ratios were 2.0 (95% CI .92 to 4.14) and 5.20 (95% CI 1.95 to 11.99) for the medium and high exposure levels, respectively. As before, interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that hydrogen sulfide represented 2/3 of the TRS (Marttila et al. 1994). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by each of the questionnaires indicated that only sulfur dioxide appeared to co-vary with TRS.

Increased respiration rates were noted when male rats were exposed to 100 ppm hydrogen sulfide for 1 hour (Higuchi and Fukamachi 1977). Increased cellularity of nasal lavage fluid was observed in male rats exposed to 10,200, or 400 ppm hydrogen sulfide for 4 hours (Lopez et al. 1987). Pulmonary alveolar macrophages from rats exposed to 200 or 400 ppm of hydrogen sulfide had an increase in cytoplasmic vacuolation. In rats, significant decreases in numbers of viable pulmonary alveolar macrophages were seen (Khan et al. 1991). Histological effects including pulmonary edema and fibrocellular alveolitis in proximal alveoli were reported in rats exposed to 83 or 439 ppm of hydrogen sulfide for 4 hours (Lopez et al. 1988a); moderate-to-massive pulmonary edema was reported in rats exposed to 375 ppm hydrogen sulfide for 4 hours (Prior et al. 1990); and pulmonary congestion was reported in rats exposed to 75 ppm hydrogen sulfide for 1 hour (Kohno et al. 199 1). No respiratory effects were found in intermediate-duration inhalation studies in rats exposed to 80 ppm hydrogen sulfide for 90 days (CIIT 1983b, 1983c), or pigs exposed to 8.5 ppm hydrogen sulfide for 17 days (Curtis et al. 1975). However, minimal-to-mild inflammation of the nasal mucosa was observed in mice after exposure to 80 ppm hydrogen sulfide for 90 days (CRT 1983a).

2. HEALTH EFFECTS

Cardiovascular Effects. Cardiovascular effects have been observed after acute exposure to high concentrations of hydrogen sulfide (Arnold et al. 1985; Audeau et al. 1985; Krekel 1964). Exposure concentrations and duration were not reported. Cardiac arrhythmia was observed in two men exposed to hydrogen sulfide for <5 minutes (Krekel 1964); normal cardiac rhythms were restored within 24 hours. Slight increases in blood pressure were observed in workers exposed by inhalation to hydrogen sulfide, but electrocardiograms were normal (Audeau et al. 1985). Other cardiovascular effects occasionally recorded in humans exposed to hydrogen sulfide by inhalation include hemodynamic instability (Osbern and Crap0 1981), tachycardia (Peters 1981; Ravizza et al. 1982; Stine et al. 1976; Thoman 1969), and hypotension (Thoman 1969). It is not known whether persons exposed to low levels of hydrogen sulfide near hazardous waste sites would have these effects.

No changes in heart rate were found in volunteers exposed to 5 ppm hydrogen sulfide for 16 minutes, after graded exercise performed to exhaustion (Bhambhani and Singh 1991). Likewise, no changes in heart rate were seen in volunteers exposed to 5 ppm hydrogen sulfide during 30 minutes of submaximal exercise (Bhambhani et al. 1994); however, effects indicative of impaired anaerobic metabolism were seen in both men and women at 10 ppm and in men at 5 ppm (Bhambhani et al. 1996b, 1997).

In a retrospective epidemiologic study using hospital discharge data from 198 l-l 990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. A significant increase in incidence was found for diseases of the circulatory system (SIR = 1.05; p = 0.001) among Rotorua residents as compared to all other New Zealand residents. Although previous monitoring information from Rotorua in 1978 showed a median concentration of hydrogen sulfide of 20 $\mu g/m^3$, with 35% of the measurements >70 $\mu g/m^3$ and 10% >400 $\mu g/m^3$ (Bates et al. 1997), the lack of monitoring information concurrent with these data makes it difficult to draw any conclusions with regard to a causal relationship between circulatory disease and hydrogen sulfide exposures.

Rabbits exposed to 72 ppm hydrogen sulfide by inhalation for 1.5 hours developed ventricular repolarization; cardiac arrhythmias developed after exposure to this concentration for 0.5 hours/day for 5 days (Kosmider et al. 1967). Cardiac arrhythmia has been reported in rats exposed to 75 ppm hydrogen sulfide for up to 60 minutes along with decreased heart rates (Kohno et al. 199 1). Marked, yet temporary, increases in blood pressure were noted in rats exposed to 100 ppm hydrogen sulfide for 1 hour (Higuchi and Fukamachi 1977).

Gastrointestinal Effects. Nausea and vomiting have been reported following inhalation exposure to high concentrations of hydrogen sulfide (Allyn 1931; Audeau et al. 1985; Deng and Chang 1987; Krekel 1964; Osbem and Crapo 1981; Thoman 1969). No histopathological changes were found in the gastrointestinal tracts of rats or mice exposed via inhalation for 90 days to 80 ppm of hydrogen sulfide (CIIT 1983a, 1983b, 1983c). In two evaluations of the acute health effects associated with communities experiencing episodes of high emissions, significant increases in the reporting of nausea as a symptom have been reported (Haahtela et al. 1992; Marttila et al. 1995). In the first study, increased emissions from a pulp mill resulted in increased concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 $\mu g/m^3$, and the 24-hour averages for the 2 days were 35 and 43 $\mu g/m^3$. Following the high exposure, and then later after a low exposure period (hydrogen sulfide level of 0.1 to 3.5 $\mu g/m^3$ for 4 hours), community responses were evaluated with a questionnaire. In this comparison, the concentration of sulfur dioxide was the same. In the later study, Marttila et al. (1995) compared community responses using six consecutive questionnaires after three predefined levels of exposure. The three exposure levels were expressed as $\mu g/m^3$ of total reduced sulfur (TRS) which was used as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <10 $\mu g/m^3$), medium (10-30 $\mu g/m^3$), and high (>30 $\mu g/m^3$) exposure. While the study found a dose-related increase in the probability of both nasal and pharyngeal symptoms, the increase in reports of nausea was significant only with the highest level of exposure. Interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that hydrogen sulfide represented 2/3 of the TRS (Marttila et al. 1994). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by the questionnaire indicated that only sulfur dioxide appeared to co-vary with TRS.

Diarrheic digestive disorder was observed in adult pigs (average body weight = 48 kg) fed hydrogen sulfide at a dose level of 15 mg/kg/day for a few days (Wetterau et al. 1964). Intermediate-duration studies did not find any gastrointestinal effects in rats (CIIT 1983b, 1983c), mice (CIIT 1983a), or pigs (Curtis et al. 1975). No effects were observed in pigs fed 3.1 mg/kg/day for 105 days. In addition, this effect was not observed in a repeat experiment utilizing pigs that weighed 18-19 kg.

Hematological Effects. Cyanosis has been reported in a number of reports of accidental exposures to high concentrations of hydrogen sulfide and is believed to result from respiratory distress (Arnold et al. 1985; Tvedt et al. 1991 a, 199 1 b). Decreased activities of the heme-synthesizing enzymes, δ-aminolaevulinic acid (ALA) synthase and heme synthase, were found in individuals exposed to 20-200 ppm of hydrogen sulfide

for from 1 minute to 3.5 hours (Jappinen and Tenhunen 1990). Few changes in hematological parameters have been reported in workers occasionally exposed to >20 ppm hydrogen sulfide (Ahlborg 195 1). Observed changes consisted of decreases in the activities of Q-aminolaevulinic acid synthase, heme synthase, and ALA dehydratase (Tenhunen et al. 1983).

Musculoskeletal Effects. In a series of reports characterizing the responses of healthy volunteers to low level, short-term exposures to hydrogen sulfide, Bhambhani and his colleagues (Bhambhani and Singh 199 1; Bhambhani et al. 1994, 1996a, 1996b, 1997) ultimately concluded that exposures to 5 or 10 ppm hydrogen sulfide during 30-minute episodes of submaximal exercise resulted in above-normal increases in blood lactate concentrations as well as changes in the level of citrate synthetase indicative of an inhibition of the aerobic capacity of exercising muscle. Men appeared to be more sensitive to this effect, showing a small response at 5 ppm where women did not show an effect until the 10 ppm level (Bhambhani et al. 1996a, 1997). The impacts seen in this short-term exposure were considered to be a minimal effect; however, it seems likely that such increases, if extended over longer periods of time, could result in increased feelings of fatigue that might compromise other activities.

An intermediate-duration study did not find any microscopic changes in the skeletal muscle or bone of rats or mice with inhalation exposure to hydrogen sulfide (CIIT 1983a, 1983b, 1983c).

Hepatic Effects. Increased activities of unspecified liver enzymes were reported in some individuals exposed by inhalation to hydrogen sulfide (Burnett et al. 1977). Insufficient data are available to predict whether exposure to low levels of hydrogen sulfide might cause hepatic effects in humans living near hazardous waste sites, but this is considered unlikely to occur.

No adverse effects on histopathology, serum protein, LDH, SGOT (AST), or alkaline phosphatase activities were reported in animals exposed via inhalation to hydrogen sulfide (CIIT 1983a, 1983b, 1983c; Curtis et al. 1975; Hayden et al. 1990a, 1990b). Maternal cholesterol was significantly increased in Sprague-Dawley rat dams exposed to 75 ppm for 7 hours a day from gestation day 6 to postpartum day 21 (Hayden et al. 1990b).

Renal Effects. No adverse renal effects have been observed in workers overcome by inhaling high levels of hydrogen sulfide (Audeau et al. 1985). Based on this data, it is considered unlikely that persons exposed to low levels of hydrogen sulfide near hazardous waste sites would develop renal effects.

No renal effects were reported in intermediate-duration inhalation studies in rats (CIIT 1983b, 1983c), mice (CIIT 1983a), or pigs (Curtis et al. 1975).

Endocrine Effects. No studies examining endocrine effects in humans after hydrogen sulfide exposure by any route are available. Inhalation of 80 ppm hydrogen sulfide for up to 90 days did not cause any changes in the pituitary, thyroid, parathyroid, or adrenal glands of rats or mice (CIIT 1983a, 1983b, 1983c).

Dermal Effects. Peeling of the facial skin was reported in one patient following probable exposure to 8-l 6 ppm of hydrogen sulfide, which was believed to be due to the irritant effect of the gas (Tvedt et al. 1991a, 1991b). ATSDR (1994) indicates that direct contact with liquefied hydrogen sulfide gas can cause frostbite.

Skin discoloration and erythema were observed in rabbits exposed by the dermal route to unspecified concentrations of hydrogen sulfide for 2 hours (Laug and Draize 1942), but no histological changes were found in the skin of rats or mice exposed to 80 ppm hydrogen sulfide for 90 days (CIIT 1983a, 1983b, 1983c).

Ocular Effects. Eye irritation (including keratoconjunctivitis, subsequent infection, punctate cornea1 erosion, blepharospasm, and photophobia) has been reported in humans exposed by inhalation to very high concentrations of hydrogen sulfide (Ahlborg 195 1; Deng and Chang 1987; Luck and Kaye 1989; Stine et al. 1976). In two evaluations of the acute health effects associated with communities experiencing episodes of high emissions of hydrogen sulfide and other pollutants associated with a pulp mill, significant increases in the reporting of eye symptoms have occurred (Haahtela et al. 1992; Marttila et al. 1995). In the first study, increased emissions from the pulp mill resulted in increased concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 $\mu g/m^3$, and the 24-hour averages for the 2 days were 35 and 43 $\mu g/m^3$. Following the high exposure, and then later after a low exposure period (hydrogen sulfide level of 0.1 to 3.5 $\mu g/m^3$ for 4 hours), community responses were evaluated with a questionnaire. Participants reported a significant increase in the prevalence of eye symptoms ($p<0.001$). In the later study, Marttila et al. (1995) compared community responses using six consecutive questionnaires after three predefined levels of exposure. The three exposure levels were expressed as $\mu g/m^3$ of total reduced sulfur (TRS) which was used as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <10 $\mu g/m^3$), medium (10-30 $\mu g/m^3$), and high (>30 $\mu g/m^3$)

exposure. The study found a dose-related increase in the prevalence of eye symptoms (probability ratios for medium and high exposures were 3.17 [95% CI 1.2 1 to 7.471], and 5.0 [95% CI 1.66 to 12.651], respectively). Interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that hydrogen sulfide represented 2/3 of the TRS (Marttila et al. 1994). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by each questionnaire indicated that only sulfur dioxide appeared to co-vary with TRS.

Because of the mixed exposures it is difficult to predict whether these symptoms would be experienced by populations near NPL sites. However, pollution patterns in geothermally active areas and near industrial facilities such as pulp mills and sour gas production facilities are likely to be similar to those reported in these studies, suggesting that populations living near such facilities could experience similar symptoms.

Body Weight Effects. No studies examining adverse effects on body weights in humans with inhalation exposure to hydrogen sulfide have been found.

Decreased body weights have been observed in female Sprague-Dawley rats and in male and female B6C3F_1 mice, but not in Fischer-344 rats, exposed by inhalation to 80 ppm of hydrogen sulfide for 90 days (CIIT 1983a, 1983b, 1983c). Pregnant rats exposed to 150 ppm of hydrogen sulfide for 14 days lost weight in one study (Saillenfait et al. 1989), but no effects on body weight were found in pigs exposed to 8.5 ppm of hydrogen sulfide via inhalation for 17 days (Curtis et al. 1975). Although very limited data are available, it is not believed that exposure to low levels of hydrogen sulfide. such as would be found in the vicinity of hazardous waste sites, would result in effects on an individual's body weight.

Total body weight gain was decreased in pigs fed hydrogen sulfide at a dose level of 6.7 mg/kg/day for 105 days (Wetterau et al. 1964). No effects on body weight gain were noted at doses of 1.5 or 3.1 mg/kg/day.

Metabolic Effects. Severe metabolic acidosis developed in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution being dumped onto acid waste material (Stine et al. 1976). In a series of reports characterizing the responses of health volunteers to low-level, short-term exposures to hydrogen sulfide during exercise, Bhambhani and his colleagues (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a, 1996b, 1997) ultimately concluded that exposures to 5 or 10 ppm hydrogen sulfide resulted in increases in blood-lactate concentrations and/or decreases in enzymes important to aerobic metabolism that

indicated inhibition of the aerobic capacity of exercising muscle. Men appeared to be more sensitive to this effect, showing a small response at 5 ppm where women did not show an effect until the 10 ppm level (Bhambhani et al. 1996a, 1997).

Pregnant rats exposed to 75 ppm of hydrogen sulfide from gestation days 1-21 had 50% increases in glucose levels (Hayden et al. 1990a). The relevance of this finding to humans is not known.

Immunological and Lymphoreticular Effects. Immunological effects have been infrequently observed in humans exposed to hydrogen sulfide and those reported were due to infection resulting from aspiration or ingestion of manure or vomit (Osbern and Crap0 198 1). No treatment-related histopathological changes were found in the spleen or lymph nodes in 2 strains of rats or in 1 strain of mice exposed by inhalation to 10.1,30.5, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No studies were found that specifically evaluated the impact of hydrogen sulfide on the cellular or humoral immune responses. Several studies evaluated the impact of hydrogen sulfide on the functioning of macrophages either in the alveolar tract (Khan et al. 1991) or the oral cavity (Mariggio et al. 1997). In neither case, however, was a significant impact on important macrophage functions observed, although Khan et al. (199 1) did observe significant depression in respiratory rates at very high concentrations of hydrogen sulfide.

Neurological Effects. The central nervous system is a target for hydrogen sulfide toxicity in humans and animals. Acute human inhalation exposure to hydrogen sulfide can result in nausea, headaches, delirium, disturbed equilibrium, poor memory, insomnia, neurobehavioral changes, loss of consciousness, tremors, and convulsions (Arnold et al. 1985; Beauchamp et al. 1984; Deng and Chang 1987; Krekel l964; McDonald and McIntosh 1951; Milby 1962; Spolyar 1951). Chronic exposure to hydrogen sulfide at presumably lower concentrations in occupational settings can cause loss of appetite, fatigue, poor memory, dizziness, and irritability (Ahlborg 195 1). The frequency of fatigue in the workers was reported to increase with length of employment and degree of exposure. A 20-month-old child exposed for nearly 1 year to at least 0.6 ppm of hydrogen sulfide had neurological symptoms including ataxia, choreoathetosis, dystonia, and inability to stand (Gaitonde et al. 1987). CT scan of the brain revealed bilateral areas of low density in the region of both basal ganglia and surrounding white matter.

In an evaluation of the acute health effects associated with episodes of high emissions of hydrogen sulfide and other pollutants associated with a pulp mill, increases in the reporting of headaches and mental symptoms

(i.e., depression, anxiety) have been reported (Haahtela et al. 1992). In this study, increased emissions from the pulp mill resulted in increased concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 $\mu g/m^3$ (96 ppb) and the 24-hour averages for the 2 days were 35 $\mu g/m^3$ (25 ppb) and 43 $\mu g/m^3$ (30 ppb). Following the high exposure, and then later after a low exposure period (hydrogen sulfide level of 0.1 to 3.5 $\mu g/m^3$ L-07 to 2.5 ppb] for 4 hours), community responses were evaluated with a questionnaire. Participants reported a significant increase in the prevalence of headache and mental symptoms($p<0.05$). In a subsequent study, Marttila et al. (1995) compared community responses using six consecutive questionnaires after three predefined levels of exposure. The three exposure levels were expressed as $\mu g/m^3$ of total reduced sulfur (TRS) which was used as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <10 $\mu g/m^3$), medium (10-30) $\mu g/m^3$, and high (>30 $\mu g/m^3$) exposure. The study found an increase in the prevalence of headaches only on the high exposure days, however, it did not reach the level of significance. Interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that hydrogen sulfide represented 2/3 of the TRS (Marttila et al. 1994). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by the questionnaires, indicated that only sulfur dioxide appeared to covary with TRS.

In a retrospective epidemiologic study using hospital discharge data from 198 l-l 990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. Although no information on hydrogen sulfide levels was presented in this report, the authors' previous work indicated that a monitoring exercise in Rotorua in 1978 found a median concentration of hydrogen sulfide of 20 $\mu g/m^3$, with 35% of the measurements >70 $\mu g/m^3$ and 10% >400 $\mu g/m^3$; additionally, elevated concentrations of mercury had previously been found in the hair of residents (Bates et al. 1997). Significant increases in incidence were found for diseases of the nervous system and sense organs (SIR = 1.11; $p <0.001$) among Rotorua residents as compared to the rest of New Zealand's residents. When incidence rates were examined for minor disease groupings within nervous system diseases, significantly increased risks were seen for other disorders of the central nervous system (SIR = 1.22; $p < 0.001$), and disorders of the peripheral nervous system (SIR = 1.35; $p <0.001$). At the level of individual diseases, statistically significant incidence ratios were found for infant cerebral palsy (SIR = 1.42; $p = 0.02$), migraine (SIR = 1.40; $p = 0.002$), other conditions of the brain (SIR = 2.50; $p <0.001$), mononeuritis of the upper limbs and mononeuritis multiplex (SIR = 1.47; $p <0.001$), and mononeuritis of the lower limbs (SIR = 2.06; $p <0.001$).

Because of the exposures to mixtures of air pollutants, it is difficult to predict whether the symptoms seen in these studies would be experienced by populations exposed to low levels of hydrogen sulfide near NPL sites. However, pollution patterns in geothermally active areas and near industrial facilities such as pulp mills and sour gas production facilities are likely to be similar to those reported in these studies, suggesting that populations living near such facilities could experience similar symptoms.

Animals acutely exposed to hydrogen sulfide at concentrations as low as 20 ppm may also have neurotoxic effects, including fatigue and somnolence (Haider et al. 1980). Rabbits exposed to 72 ppm of hydrogen sulfide for 1 .S hours lost consciousness (Kosmider et al. 1967). Loss of consciousness has also been observed in rats exposed to 800 ppm of hydrogen sulfide for 20 minutes (Beck et al. 1979). Neurochemical changes have been reported, consisting of decreased levels of total lipids and phospholipids, decreased cerebral RNA, inhibition of cytochrome oxidase, and an increase in the glial enzyme marker 2',3'-cyclic nucleotide-3'-phosphohydrolases (Haider et al. 1980; Savolainen et al. 1980). Decreased leucine uptake and acid proteinase activity were observed in mice exposed by inhalation to hydrogen sulfide for 2 hours (Elovaara et al. 1978). Inhibition of cytochrome orectic acid oxidase and a decrease in uptake in RNA were seen in mice following inhalation exposure to hydrogen sulfide for 2 hours/day, for l-4 days (Savolainen et al. 1980). Wistar rats have been shown to exhibit a decreased response rate in discriminated avoidance tasks and Sidman-type conditioned avoidance responses (Higuchi and Fukamachi 1977).

Reproductive Effects. There is some evidence that suggests that exposure to hydrogen sulfide may be associated with an increase in the rate of spontaneous abortion. Hemminki and Niemi (1982) examined the spontaneous abortion rate in relationship to maternal and paternal occupation and residential environmental pollution in an industrial community in Finland. Women who were employed in rayon textile and paper products jobs had an increased rate of spontaneous abortions ($p<0.10$), as did women whose husbands worked in rayon textile or chemical processing jobs. Pollutants examined through environmental air monitoring were sulfur dioxide, hydrogen sulfide, and carbon disulfide. Only exposure to hydrogen sulfide (in areas where the mean annual level exceeded 4 $\mu g/m^3$) was associated with an increase in spontaneous abortions in the more highly-exposed population; however, the difference was not large enough to be significant. In a recent retrospective study of spontaneous abortions in a large population of women working in the petrochemical industry in China, Xu et al. (1998) reported a significantly increased risk of spontaneous abortion with frequent exposure to petrochemicals (odds ratio of 2.7; 95% CI 1.8-3.9). When the risk associated with exposure to specific chemicals was examined, exposure to hydrogen sulfide was found to

have an odds ratio of 2.3 (95% CI = 1.2-4.4); however, no information on the level of exposure associated with such jobs was provided.

Intermediate-duration studies in rats and mice did not find any microscopic changes in male or female reproductive organs (CIIT 1983a, 1983b, 1983c). Saillenfait et al. (1989) did report a significant impact on maternal weight gain at a concentration of 150 ppm hydrogen sulfide when administered to pregnant Sprague-Dawley rats for 6 hours/day on days 6-20 of gestation. Hayden et al. (1990a, b) observed increases in maternal glucose and liver cholesterol levels following exposure of pregnant rats and their pups to hydrogen sulfide from gestation day 1 or 6 to postpartum day 21. The changes in maternal glucose levels were observed on postpartum day 21 at all exposure concentrations, (i.e., 20, 50, or 75 ppm); however, the elevations in maternal cholesterol at postpartum day 21 were only observed following exposure at the highest dose.

Developmental Effects. There are no studies of developmental effects in humans exposed to hydrogen sulfide.

Results from inhalation studies in animals suggest that hydrogen sulfide may be a developmental neurotoxicant. Neurochemical changes (in particular levels of the neurotransmitters gamma-aminobutyric acid, norepinephrine, and serotonin) and levels of the amino acids aspartate, glutamate, and taurine have been observed in various regions of the brain (Hannah et al. 1989, 1990; Skrajny et al. 1992). Histopathological alterations in the brains of rat pups exposed throughout gestation and lactation have also been reported (Hannah and Roth 1991). Some studies found no developmental effects (Hayden et al. 1990a, 1990b; Sallenfait et al. 1989).

Genotoxic Effects. The Ames test with *Salmonella typhimurium* with and without s9 liver fractions from male Syrian golden hamsters or Sprague-Dawley rats indicates that hydrogen sulfide is not a mutagen (EPA 1984). A summary of genotoxicity studies is presented in Table 2-3.

Cancer. In one residential cohort study, there was no increase in cancer incidence among persons living downwind from natural gas refineries in Alberta, Canada, from 1970 to 1984 (Schecter et al. 1989). In a similar study in Rotorua, New Zealand, Bates et al. (1998) evaluated the risk of cancer to known target organ systems of hydrogen sulfide toxicity. Rotorua uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but in their previous work

Table 2-3 Genotoxicity of Hydrogen Sulfide *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Salmonella typhimurium TA97, TA98, TA100	Reverse mutation	–	–	EPA 1984

– = negative result

these authors indicated that a monitoring exercise in 1978 found a median concentration of hydrogen sulfide for Rotorua of 20 μg/m^3, with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3 (Bates et al. 1997). Based on the cancer registry information, these researchers found a significantly increased risk of nasal cancers (SIR = 3.17; p = 0.01) among Rotorua residents as compared to the rest of the population of New Zealand. However, since this is a rare cancer, this finding was based on only four cancers. Because the population of Rotorua has a higher percentage of Maoris than the rest of New Zealand, these researchers also examined their data stratified by ethnicity and sex and found a significantly increased risk of cancers of the trachea, bronchus, and lung (SIR = 1.48; p = 0.02) among female Maoris in Rotorua as compared to female Maoris in the rest of New Zealand. Differences in smoking history between these two populations was not sufficient to explain the observed differences in risk. The authors concluded that the lack of adequate exposure information did not permit findings of causal relationships between hydrogen sulfide and cancer incidence, but that the elevated disease rates were consistent with what might be expected "...if sufficient exposures to hydrogen sulfide and/or mercury were occurring."

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children

and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Widdowson and Dickerson 1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997; Komori 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depend on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

There is little information in the available literature to judge the impacts of exposure to hydrogen sulfide on infants and children, however, it is likely that the same toxicity seen in adults will be seen in children. Acute exposures to hydrogen sulfide have caused death in adolescents as well as adults (Allyn 1931; Hagley and South; Morse et al. 1981). Gaitonde et al. (1987) reported on a toxic encephalopathy in a 20-month-old child who had long-term exposure to pollutants generated from “a burning tip” from a coal mine. Hydrogen sulfide levels as high as 0.6 ppm had been measured in the family’s housing tract, however, no information was provided about the level of other combustion products that might have been produced by the same source.

Several studies have examined the reproductive and developmental toxicity of inhaled hydrogen sulfide in animals. Saillenfait et al. (1989) observed no fetal effect in a dose range-finding developmental study in which pregnant Sprague Dawley dams were exposed to 150 ppm hydrogen sulfide for 6 hours/day from gestation day 6 until gestation day 20, even though the dams showed significant body weight loss at this dose. Hayden et. al. (1990b) found a dose-related increase in parturition time in animals exposed to 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 6 until postpartum day 2 1 and noted that at the extreme end of the range, i.e., 200 minutes, viability was decreased to about 70%. This study also found delays in pinna detachment and hair development; however, for both effects the delay was longer at the lower concentration, i.e., no dose-related increase in effects was observed.

Hannah and Roth (1991) exposed timed pregnant dams (and their pups) from day 5 postcoital, until day 21 postnatal, to either 20 or 50 ppm of hydrogen sulfide for 7 hours a day and found severe alterations in the architecture and growth patterns of the Purkinje cell dendritic fields at both doses leading these authors to conclude that exposure to low concentrations of hydrogen sulfide place "developing neurons...at risk of severe deficits."

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in

body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hydrogen sulfide are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by hydrogen sulfide are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Hydrogen Sulfide

Measurement of human blood sulfide concentrations may serve as an indicator of hydrogen sulfide exposure (Jappinen and Tenhunen 1990), but this is seldom done and is of limited use in clinical medicine. An improved method using ion selective electrodes and preconcentration of trapped sulfide in sodium hydroxide solution allows for the detection of low blood sulfide concentrations, thus making it potentially useful in nonfatal hydrogen sulfide exposures. This method was tested in workers acutely exposed to hydrogen sulfide for durations ranging from 1 minute to 3.5 hours. Hydrogen sulfide airborne concentrations were estimated to be in the range of 20-200 ppm. Some workers became unconscious as a result of the exposure. The method is most reliable if blood samples are taken no later than 2 hours after exposure to hydrogen sulfide. Urinary thiosulfate levels have been proposed as a more suitable biomarker for hydrogen sulfide exposure (Kage et al. 1992; Kangas and Savolainen 1987). An advantage of this biomarker is that it is noninvasive. Measurement of urinary thiosulfate levels allows for the monitoring of hydrogen sulfide exposure at

concentrations found in occupational settings. Urinary thiosulfate can be measured as its bromobimane complex by liquid chromatography.

The usefulness of urinary thiosulfate as an indicator of nonfatal hydrogen sulfide toxicity has been studied (Kangas and Savolainen 1987). Urinary samples for thiosulfate were obtained from volunteers exposed by inhalation to 8, 18, or 30 ppm of hydrogen sulfide for 3045 minutes (the occupational exposure limit of 10 ppm for 8 hours was never exceeded). Excretion of urinary thiosulfate increased linearly up to 15 hours postexposure. Beyond 15 hours, the urinary thiosulfate concentration remained low, possibly indicating that most of the absorbed hydrogen sulfide was metabolized or excreted within 15 hours.

Urinary thiosulfate levels as an exposure biomarker have been examined in rabbits (Kage et al. 1992). Urinary thiosulfate levels were detected in rabbit urine 24 hours after exposure to nonfatal concentrations of 100-200 ppm of hydrogen sulfide. Thiosulfate levels could be detected in the blood for up to 2 hours following exposure, whereas blood sulfide was not detectable. Measurements of thiosulfate levels in the blood, lung, or brain were found following fatal exposures to 500-l ,000 ppm of hydrogen sulfide in experimental animals.

2.7.2 Biomarkers Used to Characterize Effects Caused by Hydrogen Sulfide

Alterations in blood heme metabolism have been proposed as a possible indicator of the biological effects of hydrogen sulfide (Jappinen and Tenhunen 1990), but this does not relate to the mechanism of toxicity in humans. The activities of the enzymes of heme synthesis, i.e., delta-aminolevulinic acid synthase (ALA-S) and heme synthase (Haem-S), were examined in 21 cases of acute hydrogen sulfide toxicity in Finnish pulp mill and oil refinery workers. Subjects were exposed to hydrogen sulfide for periods ranging from approximately 1 minute to up to 3.5 hours. Hydrogen sulfide concentrations were considered to be in the range of 20-200 ppm. Several subjects lost consciousness for up to 3 minutes, Activities of ALA-S and Haem-S were decreased after exposure to hydrogen sulfide. However, the changes in heme metabolism are not specific for hydrogen sulfide, and other sulfur-containing compounds such as methyl mercaptan can produce similar effects.

Potential biomarkers for neurological effects of hydrogen sulfide include indices of cortical, hippocampal, brain stem, basal ganglia, and diencephalon dysfunction. An oil-field worker who became unconscious following exposure to hydrogen sulfide had a diminished vibration sense, delayed visual reaction times,

abnormal balance with eyes closed, slow blink reflex latency, impaired verbal and visual recall, and decreased cognitive performance (Kilburn 1993). Cortical function tests revealed deficits in verbal abstraction, attention, and short-term retention in a hydrogen sulfide-poisoned patient (Stine et al. 1976). A 5-year neuropsychological re-examination of patients who lost consciousness after hydrogen sulfide exposure revealed neurological impairment (Tvedt et al. 1991 b); memory and motor function were most affected. Computed tomograms of the brain of a child who had subacute encephalopathy following chronic exposure to hydrogen sulfide revealed abnormalities in the basal ganglia (Gaitonde et al. 1987). Such neurological effects are not specific for hydrogen sulfide and could indicate exposure to other neurotoxic substances.
For more information on biomarkers for renal and hepatic effects of chemicals, see the ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990), and for information on biomarkers for neurological effects, see OTA (1990).

2.8 INTERACTIONS WITH OTHER CHEMICALS

In a group of Belgian viscose rayon workers exposed to 0.14 or 6.4 ppm of hydrogen sulfide and at least 26 mg/m^3 of carbon disulfide, the incidence of eye irritation was significantly higher in all hydrogen sulfide-exposed workers than in unexposed controls (Vanhoorne et al. 1995). Control for confounders such as cigarette smoke was not performed (Vanhoorne et al. 1995). Simultaneous exposure of Sprague-Dawley rats to 500 ppm of carbon disulfide and 50 ppm of hydrogen sulfide 5 days/week, for 25 weeks, had no interactive effect on sensory tail nerve conduction velocities (SNCV) or motor tail nerve conduction velocities (MNCV) (Gagnaire et al. 1986). Additionally, the amount of 2-thio-thiazolidine-4-carboxylic acid, a urinary metabolite of carbon disulfide excreted in urine after exposure to carbon disulfide, was unaffected by hydrogen sulfide exposure (Gagnaire et al. 1986). In a series of reproductive and developmental studies in which albino rats were exposed to hydrogen sulfide and carbon disulfide, both pre- and postimplantational lethality as well as developmental anomalies of the genito-urinary and skeletal systems were reported (Bariliak et al. 1975). However, in some cases these effects occurred in conjunction with maternal toxicity. It is not clear whether the reported concentration (10 mg/m^3) to which the animals were exposed includes both hydrogen sulfide and carbon disulfide or represents individual concentrations of each chemical.

There appears to be some evidence that ethanol can increase the effects of hydrogen sulfide. In 6 cases, less hydrogen sulfide was needed for toxic effects to be observed when workers had consumed alcohol 16-24 hours earlier (Poda 1966).

Much of the occupational data on hydrogen sulfide comes from studies of pulp and paper mill workers who were exposed to other compounds in addition to hydrogen sulfide. An increase in chronic or recurrent headache was noted in Finnish pulp workers who were exposed simultaneously to hydrogen sulfide, methyl mercaptans, and sulfur dioxide (Kangas et al. 1984). Peak concentrations of the chemicals, up to 20 ppm hydrogen sulfide, were believed to be responsible for the occurrence of the symptoms, rather than the lower mean concentrations. A respiratory survey of almost 2,000 Canadian pulp and paper mill workers did not show any increases in the'prevalence of respiratory symptoms or pulmonary function abnormalities among exposed workers (Chan-Yeung et al. 1980). Mean exposure concentrations of toxicants measured in this study were 0.05 ppm hydrogen sulfide, 0.3 ppm sulfur dioxide, 8.3 ppm carbon monoxide, 0.8 ppm total particulates, and <0.05 ppm chlorine.

No changes in body weight or microscopic changes in respiratory tract, eye, or visceral organs were noted in crossbred pigs inhaling 2 ppm of hydrogen sulfide and 50 ppm of ammonia continuously for 19 days when compared to controls (Curtis et al. 1975). The toxicity of hydrogen sulfide after dermal exposure was found to be enhanced by dermal exposure to ammonia (Laug and Draize 1942).

Male Wistar rats were administered 330 or 660 mg/kg of ethanol intraperitoneally 30 minutes before being exposed to 800 ppm of hydrogen sulfide for a maximum of 20 minutes, which was a potentially fatal hydrogen sulfide exposure (Beck et al. 1979). Mean times to unconsciousness in animals that were exposed to hydrogen sulfide with ethanol pretreatment at either of these dose levels were approximately 35% less than times to unconsciousness without ethanol pretreatment (Beck et al. 1979). The clinical relevance of these findings, which used potentially fatal doses of both ethanol and hydrogen sulfide, is unclear.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hydrogen sulfide than will most persons exposed to the same level of hydrogen sulfide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of hydrogen sulfide, or compromised function of target organs affected by hydrogen sulfide. Populations who are at greater risk due to their unusually high exposure to hydrogen sulfide are discussed in Section 5.7, Populations With Potentially High Exposure.

Because hydrogen sulfide severely limits oxidative metabolism by inhibiting cytochrome oxidase in mitochondrial respiration, tissues with the highest oxygen demands, such as cardiac and nervous tissues, are the most sensitive to exposure. Although psychological effects have not been noted as sequelae of hydrogen sulfide exposure, at least one study has suggested that persons with neuropsychiatric disorders might be more susceptible (Poda 1966). Persons with pre-existing cardiac or other nervous system disorders might be more susceptible.

Some asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes had changes in pulmonary function tests indicative of bronchial obstruction, although the exposed group as a whole did not show a statistically significant change in these parameters (Jappinen et al. 1990). Asthmatics have also been found to have a worsening of their condition upon exposure to odors (Shim and Williams 1986). Although this has not been tested with exposure to hydrogen sulfide, it might be reasonably anticipated due to the malodorous quality of hydrogen sulfide gas. These findings suggest that some asthmatics may be more sensitive to hydrogen sulfide than the general population.

It has been suggested that workers with tympanic membrane defects such as perforated eardrums or tympanomaxillary shunts (ear tubes) might be at increased risk during hydrogen sulfide exposure. An analysis of the anatomy and physiology of the inner ear by Ronk and White (1985) concluded that tympanic membrane defects do not significantly affect the efficacy of respiratory protection in hydrogen sulfide exposure.

Evidence from a number of studies suggests that hydrogen sulfide, endogenously produced by bacteria in the digestive tract, may play a role in the etiology of ulcerative colitis (Babidge et al. 1998; Pitcher and Cummings 1996; Roediger et al. 1997). It is unclear whether patients are affected due to the excess production of hydrogen sulfide or the inability to detoxify it as effectively as controls. Irrespective of mechanism, it seems likely that individuals already suffering from hydrogen sulfide-associated toxicity will be at higher risk from further hydrogen sulfide exposures. Ulcerative colitis is usually found in adults, so children are less susceptible.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to hydrogen sulfide. However, because some of the treatments discussed may be experimental and

unproven, this section should not be used as a guide for treatment of exposures to hydrogen sulfide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to hydrogen sulfide:

ATSDR. 1994. Hydrogen sulfide. Managing hazardous materials incidents. Volume III. Medical management guidelines for acute chemical exposures. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Ellenhorn MJ. 1997. Hydrogen sulfide. In: Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams and Wilkins.

Hall AH. 1996. Systemic asphyxiants. In: Rippe JM, Irwin RS, Fink MP, Cerra FB. ed. Intensive care medicine, 3rd edition. Boston, MA: Little, Brown, and Company.

There is no proven antidote for hydrogen sulfide poisoning. Treatment consists of supportive measures such as evaluating and supporting airway, breathing, and circulation (ATSDR 1994). Sodium nitrite may or may not be an effective antidote, but if proper precautions in administration are observed, intravenous administration of sodium nitrite may help some hydrogen sulfide poisoned persons (Hall 1996; Hall and Rumack 1997). Hyperbaric oxygen therapy is controversial, but it may be effective for patients not treated successfully by other measures (ATSDR 1994).

There are no pediatric-specific methods for reducing toxic effects.

2.10.1 Reducing Peak Absorption Following Exposure

There are no specific methods available to reduce the absorption of hydrogen sulfide following exposure. Supportive treatment includes artificial respiration if respiration is depressed; administration of oxygen; and standard medical treatment for eye irritation, pulmonary edema, seizures, and hypotension (Sorokin 1993).

2.10.2 Reducing Body Burden

There are no known methods for reducing the body burden of hydrogen sulfide, although adopting a diet low in sulfur-containing, exogenously acquired foods, e.g., milk and cheese, has been shown to reduce the endogenous production of hydrogen sulfide (Roediger et al. I997).

The major metabolic pathway of hydrogen sulfide is the oxidation of the sulfide to sulfate in the liver (Beauchamp et al. 1984). Methylation also serves as a detoxification route. Hydrogen sulfide is excreted primarily as sulfate (either as free sulfate or as thiosulfate) in the urine.

Methemoglobin induction with sodium nitrite may be used to treat hydrogen sulfide poisoning in humans (Ellenhorn 1997), although it is unclear that induction of methemoglobin is the mechanism of antidotal action of sodium nitrite in this poisoning. However, it is thought that methemoglobin may attract sulfide, forming sulfmethemoglobin, which undergoes spontaneous detoxification in the body (Ellenhorn 1997). This is discussed further in Section 2.10.3.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Hydrogen sulfide inhibits mitochondrial cytochrome oxidase, resulting in disruption of the electron transport chain and impairing oxidative metabolism. Nervous and cardiac tissues, which have the highest oxygen demand (e.g., brain and heart), are especially sensitive to disruption of oxidative metabolism (Ammann 1986; Hall 1996).

Nitrites such as amyl and sodium nitrites have been used in the treatment of hydrogen sulfide poisoning, and the mechanism of therapeutic action may involve the prevention or reversal of cytochrome oxidase inhibition (Ellenhorn 1997; Hall 1996; Hoidal et al. 1986; Osbern and Crapo 1981; Reiffenstein et al. 1992). It has been postulated that nitrites induce methemoglobin, which inactivates sulfide, thereby preventing cytochrome oxidase inhibition and reactivating aerobic respiration (Ellenhorn 1997; Hall 1996). However, sulfide in oxygenated blood is short-lived and the induction of methemoglobin after about 15 minutes postexposure may not assist the patient (Ellenhorn 1997).

Oxygen treatment may be used after hydrogen sulfide poisoning, although its use is somewhat controversial (Ellenhorn 1997; Ravizza et al. 1982). Smith et al. (1976) found that oxygen was not useful as an antidote to

hydrogen sulfide poisoning in mice. High intracellular oxygen pressure may result in nonenzymatic oxidation of cytochrome oxidase, and oxygen may release sulfide from cytochrome oxidase binding by a concentration effect (Ravizza et al. 1982). Hyperbaric oxygen therapy has been suggested for cases not responding to supportive care and nitrite treatment, but its clinical efficacy has not yet been determined (Ellenhorn 1997; Hall 1996).

In one case report (Schneider et al. 1998) where an individual suffered long-term (4 years later) neuropsychological sequelae from a "knock-down" exposure to hydrogen sulfide, treatment with two drugs, Ritalin and Cyclert, partially alleviated some of the observed deficits in cognitive function and general cognition; these drugs enhance dopaminergic functioning. However, more examples of the efficacy of this treatment are required.

2.11 ADEQUACY OF THE DATABASE

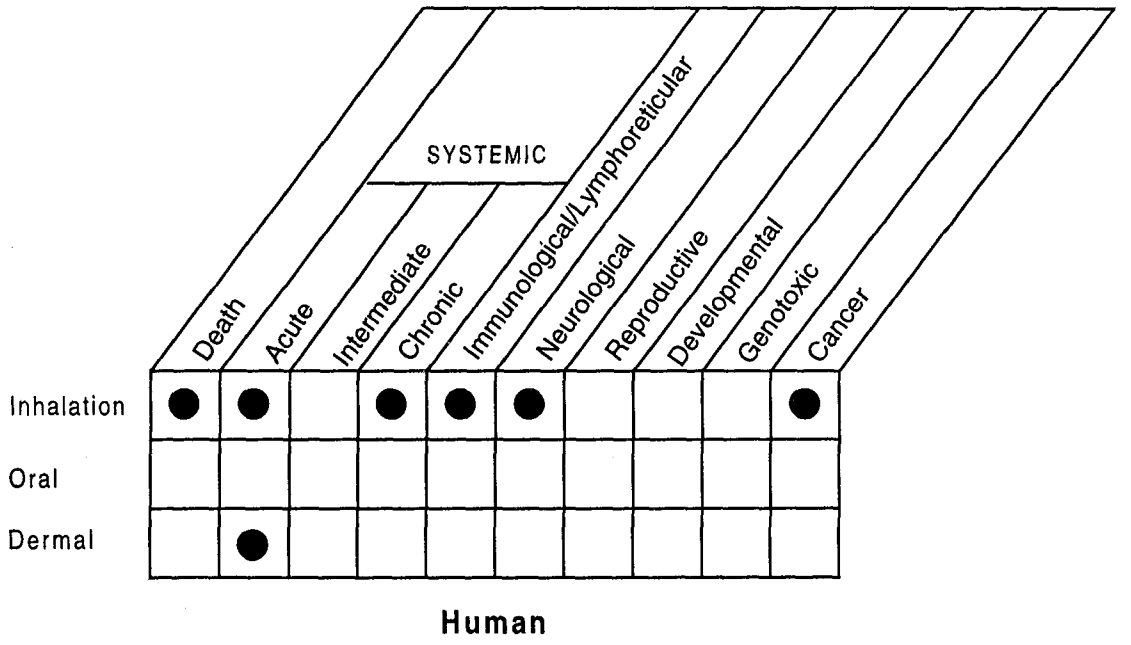
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hydrogen sulfide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrogen sulfide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

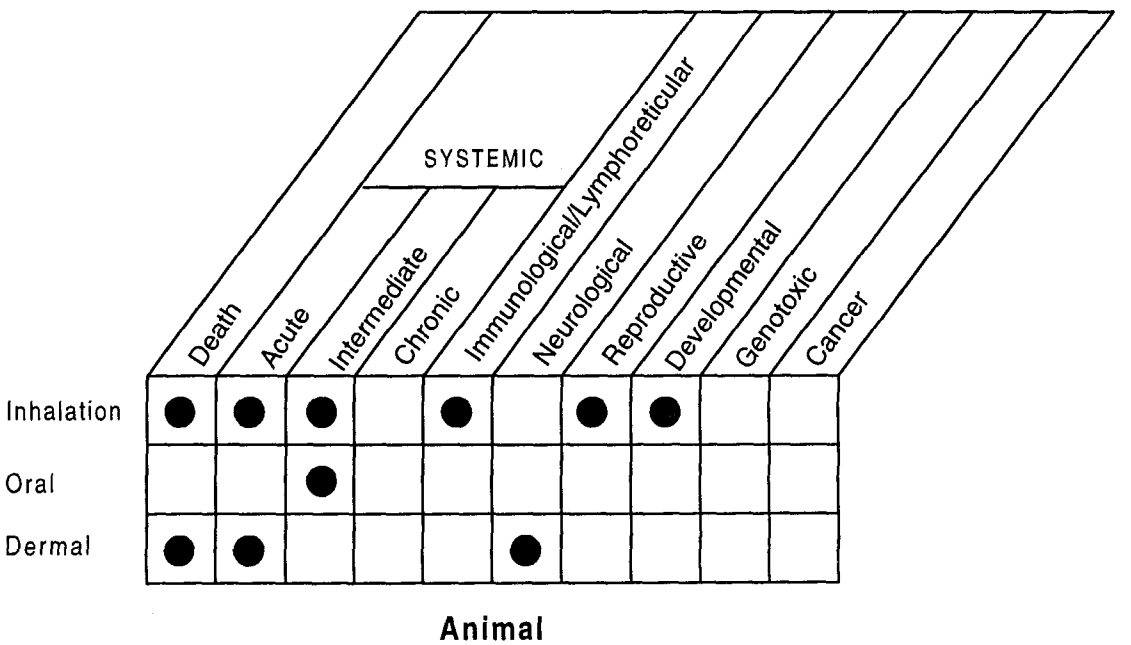
2.11.l Existing Information on Health Effects of Hydrogen Sulfide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hydrogen sulfide are summarized in Figure 2-5. This figure illustrates the existing information concerning the health effects of hydrogen sulfide; each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the

FIGURE 2-5. Existing Information on Health Effects of Hydrogen Sulfide



Human



Animal

● Existing Studies

quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. There are numerous case reports of human fatalities (Adelson and Sunshine 1966; Allyn 1931; Breysse 1961; Campanya et al. 1989; Deng and Chang 1987; Freireich 1946; Hagley and South; Morse et al. 1981; Osbern and Crapo 1981; Parra et al. 1991) or survivors who developed immediate as well as delayed neurological effects (Deng and Chang 1987; Kilburn 1993, 1997; Krekel 1964; McDonald and Mclntosh 1951; Milby 1962; Schneider 1998; Spolyar 1951) following acute-duration hydrogen sulfide inhalation exposure. Estimates of exposure concentrations were not often reported in these studies. Cardiac arrhythmia has also been reported in workers exposed to hydrogen sulfide (Krekel 1964). Experimental exposure studies in which subjects were exposed to hydrogen sulfide for 15-30 minutes did not identify any respiratory or cardiovascular effects in healthy subjects at 5 or 10 ppm (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a). Pulmonary function tests were normal in workers exposed to up to 10 ppm hydrogen sulfide (Jappinen et al. 1990). Evidence of bronchial obstruction was observed in 2 of 10 asthmatics exposed to 2 ppm of hydrogen sulfide, although the group as a whole had no significant change in these parameters (Jappinen et al. 1990). Based on a LOAEL of 2 ppm for respiratory effects on bronchial obstruction in the Jappinen et al. (1990) study, an acute-duration inhalation MRL of 0.07 ppm was derived. Further acute-duration exposure studies in humans are needed to provide more support for this LOAEL. In addition, studies that include asthmatic subjects are needed to confirm that they are indeed a sensitive subpopulation. Because hydrogen sulfide gas is an eye irritant (Ahlborg 1951; Luck and Kay 1989), such studies should also monitor ocular effects. Additional studies of the delayed consequences of acute exposures are also needed as well as more information as to effective treatments such as reported in the Schneider et al. (1998) study.

Acute-duration inhalation studies of hydrogen sulfide in animals have reported death (Beck et al. 1979; Khan et al. 1990; Lopez et al. 1989; Nagata et al. 1990; Prior et al. 1988, 1990; Smith and Gosselin 1964; Tansy et al. 1981), respiratory (Green et al. 1991; Khan et al. 1990; Kohno et al. 1991; Lopez et al. 1987, 1988a, 1988b; Prior et al. 1990), cardiovascular (Higuchi and Fukamachi 1977; Kohno et al. 199 1; Kosmider et al.

1967), immunological/lymphoreticular (Khan et al. 1991), and neurological effects (Beck et al. 1979; Haider et al. 1980; Higuchi and Fukamachi 1977; Kosmider et al. 1967; Lopez et al. 1988b). Additional acuteduration inhalation animal studies are needed to further define any direct cardiovascular effects of hydrogen sulfide as opposed to those due to hypoxia.

Data are not sufficient for the development of an acute-duration oral MRL. The only oral study of hydrogen sulfide is a study in which a diarrheic digestive disorder was observed in pigs fed hydrogen sulfide at 15 mg/kg/day for "a few days" (Wetterau et al. 1964). Acute dermal exposure of animals has resulted in death (Laug and Draize 1942). In addition to a lack of route-specific toxicity data, insufficient pharmacokinetic data are available to support the identification of target organs across routes of exposure. However, although oral and dermal data regarding the effects of hydrogen sulfide are very limited, human exposure would be expected to be principally by inhalation.

Intermediate-Duration Exposure. Intermediate-duration studies in humans are fairly limited and virtually all are complicated by exposures to other chemicals as well as rarely being accompanied with adequate exposure assessment. Additional epidemiologic studies, particularly prospective or case-control, of populations exposed environmentally to various levels of hydrogen sulfide (where other pollutants are monitored and ideally, do not vary) are needed.

A series of 90-day inhalation studies in rats (CIIT 1983b, 1983c) reported significantly decreased body weights in Sprague-Dawley female rats at 80 ppm but not in male Sprague-Dawley (CIIT 1983c) nor in either sex of Fischer 344 rats (CIIT 1983b). In a companion study with $B6C3F_1$ mice, a significant increase in the incidence of inflammation of the nasal mucosa was observed at a dose level of 80 ppm but not at 30.5 ppm. This NOAEL of 30.5 ppm for respiratory effects forms the basis of the intermediate duration MRL of 0.03. The NOAEL was adjusted for intermittent exposure and the $NOAEL_{[HEC]}$ is calculated. An uncertainty factor of 30 is then applied, 3 for extrapolating from animals to humans and 10 for human variability.

No histopathological effects were found in respiratory tract tissues or organs when pigs were exposed to 8.5 ppm hydrogen sulfide continuously for 17 days (Curtis et al. 1975). Additional effects reported in rats following inhalation exposure to hydrogen sulfide include increased glucose in lactating rats (Hayden et at. 1990a), increased liver cholesterol in female rats exposed during gestation and lactation (Hayden et al. 1990b), and weight loss in pregnant rats (Saillenfait et al. 1989).

2. HEALTH EFFECTS

The only oral study of hydrogen sulfide is a study in pigs in which decreased body weights were observed in pigs fed hydrogen sulfide in the diet at 6.7 mg/kg/day for 105 days (Wetterau et al. 1964). No effects were observed at a dose of 3.1 mg/kg/day. However, because this study lacks details and there is no supporting data, no intermediate-duration MRL was derived. Additional intermediate-duration oral studies of hydrogen sulfide are needed to provide support for this study.

No intermediate-duration dermal studies of hydrogen sulfide were identified. As significant human dermal exposure to hydrogen sulfide is unlikely, dermal exposure studies should not be a high priority. However, no pharmacokinetic data are available that might support the identification of target organs across routes of exposures in the absence of route-specific toxicity data.

Chronic-Duration Exposure and Cancer. A study of workers exposed to hydrogen sulfide at concentrations that often exceeded 20 ppm reported slight irritation of the mucous membranes, fatigue, loss of appetite, headache, irritability, poor memory, and dizziness (Ahlborg 1951). Pulp industry workers exposed to 8-hour TWA concentrations of 0.05-5.2 ppm hydrogen sulfide had no signs of clinical anemia but did show decreases in ALA-S, Heme-S, and ALA dehydratase activities, as well as erythrocyte protoporphyrin (Tenhunen et al. 1983). This study was confounded by workers' exposure to other compounds such as methyl mercaptan and dimethylsulfide, inadequately described controls, and an absence of statistical analysis. A study of persons living near a paper mill who were exposed to hydrogen sulfide showed increased eye irritation and some respiratory effects compared to nonexposed individuals; however, they were also exposed to methyl mercaptan and sulfur dioxide (Jappinen et al. 1990). There was no increase in cancer incidence noted in a residential cohort study of persons living downwind from natural gas refineries (Schecter et al. 1989), but an increased risk of nasal cancers was found in a population residing in a location of high geothermal activity (Bates et al. 1998).

Additional chronic-duration studies of hydrogen sulfide, including studies of the carcinogenic potential of hydrogen sulfide in humans and animals by any route of exposure, have not been performed. Follow-up epidemiological studies of populations environmentally exposed to hydrogen sulfide due to proximity of pulp mills, sour gas plants, or geothermal energy sources are needed but only if they are accompanied by adequate exposure measurements. As limited genotoxicity studies suggest that hydrogen sulfide is unlikely to be a carcinogen, lifetime carcinogenicity studies in animals should not be a high priority. In the absence of routespecific toxicity data and route-specific pharmacokinetic data, it is not possible to identify target organs across routes of exposure.

Genotoxicity. No mutagenicity was observed in Ames assays using *S. typhimurium* strains TA97, TA98, and TAl 00, either with or without S9 liver fractions from male Syrian golden hamsters or Sprague-Dawley rats (EPA 1984). Specific concentrations of hydrogen sulfide gas was limited because of its solubility in ethanol, which was the test solvent. The highest dose that could be obtained was 1,750 µg/plate. Other studies using hydrogen sulfide in the gaseous state are needed for testing higher doses.

Reproductive Toxicity. The findings in two studies (Hemminki and Niemi 1982; Xu et al. 1998) that exposures to hydrogen sulfide are associated with an increased risk of spontaneous abortion warrants further investigation. A well-designed case-control study is needed in which exposure is well characterized in order to ascertain whether this is indeed an effect of concern or merely an anomaly. Additional epidemiologic studies of other reproductive effects are also needed. No treatment-related histopathological changes were found in the male or female reproductive organs of rats (CUT 1983b, 1983c) or mice (CIIT 1983a) exposed to hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days. Studies of reproductive function in animals exposed to hydrogen sulfide are needed, including one or more that would serve as a surrogate for detecting spontaneous abortions, and a multilitter or multigeneration study in several animal species after exposure to hydrogen sulfide by inhalation are needed.

Developmental Toxicity. No studies were located regarding developmental effects in humans following hydrogen sulfide exposure.

Developmental effects were not observed in rats exposed to hydrogen sulfide by inhalation at concentrations that resulted in maternal body weight loss (Saillenfait et al. 1989), increased maternal blood glucose levels (Hayden et al. 1990a), or increased cholesterol content of the maternal liver (Hayden et al. 1990b). Purkinje cell path length in offspring of exposed rats was increased compared to controls (Hannah and Roth 1991). Changes in amino acid levels (Hannah et al. 1989, 1990) and serotonin and epinephrine levels (Skrajny et al. 1992) in the brain were found in the offspring of rats exposed by inhalation to hydrogen sulfide during gestation. Studies regarding the developmental toxicity of hydrogen sulfide following oral or dermal exposure were not located.

As hydrogen sulfide is a neurotoxic agent, an inhalation study examining potential developmental neurotoxicity is needed. Such studies should include a battery of tests to examine the function of the nervous

system in the offspring of animals exposed to hydrogen sulfide during gestation or for various periods before adulthood.

Immunotoxicity. Immunological effects infrequently observed after human hydrogen sulfide exposure appear to result from infection due to the aspiration or ingestion of manure or vomit (Osbern and Crapo 1981). No treatment-related histopathological changes were found in the spleen or lymph nodes of rats (CIIT 1983b, 1983c) or mice (CIIT 1983a) exposed to hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days. Although the number of pulmonary alveolar macrophage cells was not influenced by hydrogen sulfide exposure, the number of viable cells was significantly decreased with exposure to 400 ppm (Khan et al. 1991). When pulmonary alveolar macrophage cells were treated with Zymosan to stimulate respiration rates, there was no stimulation of respiration in cells from animals exposed to 200 or 400 ppm of hydrogen sulfide for 4 hours (Khan et al. 1991). Immunological effects have not been studied in humans or animals following oral or dermal exposure to hydrogen sulfide.

Additional studies of immune function in animals exposed to hydrogen sulfide by inhalation are needed. A bacterial and/or viral challenge study would be especially useful to determine whether exposure to hydrogen sulfide increases susceptibility to infection.

Neurotoxicity. The nervous system is a target organ for hydrogen sulfide. Effects of acute inhalation exposure in humans include nausea, headaches, delirium, disturbed equilibrium, poor memory, loss of consciousness, tremors, and convulsions (Arnold et al. 1985; Deng and Chang 1987; Krekel 1964; McDonald and McIntosh 195 1; Milby 1962; Spolyar 195 1). Acute effects observed in animals include fatigue, somnolence (Haiden et al. 1980), and loss of consciousness (Kosmider et al. 1967). Limited data from chronically exposed workers indicate that loss of appetite, fatigue, poor memory, dizziness, and irritability may result (Ahlborg 195 1; Krekel 1964). Studies in rats have shown decreases in performance of discriminated avoidance tasks after exposure to hydrogen sulfide (Higuchi and Fukamachi 1977). The potential neurotoxicity of hydrogen sulfide following oral or dermal exposures has not been characterized. The transplacental neurological effects of hydrogen sulfide exposure are unknown. There is no reason to suspect that the neurotoxic effects observed after hydrogen sulfide exposure are species-specific, and insufficient data are available to determine whether effects are route-specific. Well-designed studies investigating neurotoxic effects in animals following oral or dermal exposure, and chronic neurotoxic effects after inhalation exposure are needed to determine the,effects that might be seen in exposed humans.

Epidemiological and Human Dosimetry Studies. Published reviews have addressed the duration of exposure and concentrations of hydrogen sulfide resulting in death and serious effects in humans (Beauchamp et al. 1984; EPA 1978; NIOSH 1977a; WHO 1981). The limited chronic-duration epidemiological studies (Ahlborg 1951; Jappinen et al. 1990; Schecter et al. 1989; Tenhunen et al. 1983) have identified approximate exposure concentrations, but exposure assessment was not sufficient to divide the study population into more than one exposure group. Epidemiology studies examining the potential effects of chronic inhalation exposure to various hydrogen sulfide concentrations are needed. There are known populations that have unusually high exposure to hydrogen sulfide.

Biomarkers of Exposure and Effect

Exposure. Both blood sulfide concentrations (Jappinen and Tenhunen 1990) and urinary thiosulfate concentrations (Kage et al. 1992; Kangas and Savolainen 1987) have been proposed as indicators of hydrogen sulfide exposure. Obtaining background levels of blood sulfide in a population should not be problematic, although blood samples to determine sulfide concentrations must be obtained within 2 hours of exposure to hydrogen sulfide. Similarly, urinary thiosulfate levels can be obtained for the background population, Further study is needed to correlate airborne exposure concentrations with blood sulfide and thiosulfate levels. Additional biomarkers of exposure for hydrogen sulfide are not needed, although the above are of limited utility in clinical medicine. Additional studies of variations in the endogenous production of hydrogen sulfide and its detoxification and distribution are needed in order to determine whether variations in susceptibility can be identified on the basis of such traits.

Effect. Potential biomarkers of the subclinical effects of hydrogen sulfide are decreases in the activities of the heme synthesis enzymes, ALA-S and Haem-S (Jappinen and Tenhunen 1990). These effects have nothing to do with the mechanism of toxicity, however. Neurological indices are also used as biomarkers of effect for hydrogen sulfide (Gaitonde et al. 1987; Kilburn 1993; Stine et al. 1976; Tvedt et al. 1991b). These effects are not specific for hydrogen sulfide, and further study is needed to correlate these effects with blood sulfide and urinary thiosulfate levels.

Absorption, Distribution, Metabolism, and Excretion. Hydrogen sulfide is absorbed through the lungs and can be absorbed in minor quantities through the gastrointestinal tract and intact skin (Kohno et al. 1991; Laug and Draize 1942; Wetterau et al. 1964). Hydrogen sulfide is also produced endogenously in many tissues, e.g., liver, kidney, and heart, as a break-down product of cysteine metabolism. Thus, hydrogen

sulfide is widely distributed in the body. Sulfides have been found in the heart, liver, blood, brain, lungs, spleen, and kidneys of humans who died after accidental inhalation exposure (Kohno et al. 1991). However, there are no studies that have tracked the quantitative absorption or endogenous production of hydrogen sulfide nor quantified the differences in its distribution in the various tissues to follow absorption of an external dose. No data are available on distribution after oral or dermal exposure to hydrogen sulfide.

Hydrogen sulfide is metabolized through three pathways: oxidation, methylation, and reactions with metalloproteins or disulfide-containing proteins (Beauchamp et al. 1984). Although the major metabolic pathway for detoxification is oxidation of the sulfide to sulfate in the liver, methylation also serves to detoxify hydrogen sulfide (EPA 1987a; Weisiger and Jakoby 1980). The major oxidation product of hydrogen sulfide is thiosulfate, which is then converted to sulfate and excreted in the urine (Bartholomew et al. 1980; Kage et al. 1992; Kangas and Savolainen 1987). The primary location for the oxidation reaction is the liver (Bartholomew et al. 1980).

The qualitative data on the absorption, distribution, metabolism, and excretion of hydrogen sulfide in humans and animals are well known. Quantitative data are generally lacking. Additional animal data through collection by quantitative measurements are collected are needed, as well as data on changes in these parameters with exposure.

Comparative Toxicokinetics. PBPK models have not been developed to compare the toxicokinetics of hydrogen sulfide in humans and animals. Studies providing quantitative data necessary to develop PBPK models would be useful.

Methods for Reducing Toxic Effects. Other than removing the subject from exposure, there is no specific method to reduce the absorption of hydrogen sulfide. There are no known methods for reducing the body burden of hydrogen sulfide, although reducing the intake of sulfhydryl-containing amino acids has been shown to reduce endogenous production. Amyl and sodium nitrites have been used as antidotes for hydrogen sulfide. However, caution in the use of nitrites has been recommended since nitrites can add to the preexisting histotoxic hypoxia from hydrogen sulfide (Ravizza et al. 1982). Oxygen treatment, which may result in nonenzymatic oxidation of cytochrome oxidase, may also be used in the treatment of hydrogen sulfide poisoning (Hall 1996; Ravizza et al. 1982).

There is a need to develop an antidote for hydrogen sulfide poisoning, especially since it has a high knockdown potency. Additional research into the safe use of oxygen as an antidote for hydrogen sulfide poisoning is needed. Studies examining methods to enhance the oxidation or methylation of hydrogen sulfide to increase the elimination might also be useful. Further studies of the efficacy of drugs such as Retalin and Cyclert to treat the long-term neuropsychological effects of a knock-down exposure are needed.

Children's Susceptibility

There is only limited information available by which to assess the potential toxicity of hydrogen sulfide to children and infants. Several case reports suggest that adolescents respond much like adults to high dose acute exposures (Allyn 1931; Morse et al. 1981; Hagley and South 1983), but there is no information with which to determine whether the long-term consequences of such exposures differ for adolescents versus adults, nor is rhere any information on the effects of hydrogen sulfide exposures in children and very little information on infants. Several developmental toxicity studies indicated that the exposure of pregnant rats and their pups to hydrogen sulfide resulted in structural and biochemical changes in the brain (Hannah et al. 1989, 1991; Hannah and Roth 1991). Subsequent work showed that many of the biochemical changes were transient, however, no studies were found that evaluated the behavioral consequences of these changes. Thus, a variety of studies are needed in order co determine whether children and infants are at risk from neurological deficits following hydrogen sulfide exposures in utero or during childhood and adolescence; information from such studies are also needed in order to determine whether children are more sensitive to hydrogen sulfide exposure.

2.11.3 Ongoing Studies

The American Petroleum Industry is currently sponsoring research on the toxicology of hydrogen sulfide. These studies include examinations of neurotoxicology, reproductive and developmental toxicology (including developmental neurotoxicity), and the development of a PBPK model.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of hydrogen sulfide is located in Table 3-l. This information includes synonyms, chemical formula and structure, and identification numbers.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of hydrogen sulfide is located in Table 3-2.

With regard to the odor threshold for hydrogen sulfide, it should be noted that although odor can be perceived at 0.5 ppb in air, olfactory fatigue can occur at concentrations of 100 ppm or greater causing a loss of odor perception (Leonardos et al. 1969).

TABLE 3-1. Chemical Identity of Hydrogen Sulfide

Characteristic	Information	Reference
Chemical name	Hydrogen sulfide	HSDB 1998
Synonym(s)	Hydrosulfuric acid; stink damp; sulfur hydride; sulfurated hydrogen; dihydrogen monosulfide; dihydrogen sulfide; sewer gas	HSDB 1998
Registered trade name(s)	No data	Budavari et al. 1996; HSDB 1998
Chemical formula	H_2S	OHM/TADS 1998
Chemical structure	H – S – H	HSDB 1998
Identification numbers:		
CAS registry	7783-06-4	HSDB 1998
NIOSH RTECS	MX1225000	RTECS 1998
EPA hazardous waste	U135	HSDB 1998
OHM/TADS	7216752	OHM/TADS 1998
DOT/UN/NA/IMCO shipping	UN1053; IMO 2.1	HSDB 1998
HSDB	576	HSDB 1998
NCI	No data	HSDB 1998

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Hydrogen Sulfide

Property	Information	Reference
Molecular weight	34.08	Budavari et al. 1996
Color	Colorless	ACGIH 1991
Physical state	Gas	Budavari et al. 1996
Freezing point	-85.49°C	Budavari et al. 1996
Boiling point	-60.33°C	Budavari et al. 1996
Specific gravity	1.192	ACGIH 1991
Density at 0°C, 760 mmHg:	1.5392 g/L	Budavari et al. 1996
Odor	Characteristic of rotten eggs	Budavari et al. 1996
Odor threshold:		
Water	0.000029 ppm	Amoore and Hautala 1983
Air	0.5 ppb	Leonardos et al. 1969
Solubility:		
Water at 20°C	One gram in 242 mL	Budavari et al. 1996
Organic solvent(s)	Alcohol, ether, glycerol, gasoline, kerosene, crude oil, carbon disulfide	HSDB 1998; Budavari et al. 1996
Partition coefficients:		
Log K_{ow}	Not applicable	
Log K_{oc}	Not applicable	
Vapor pressure at 21.9°C	1929 kPa; 14,469 mmHg	Lide and Frederikse 1993
Acid dissociation:	$H_2S \rightleftharpoons H^+ + HS^-$ (1′); $HS^- \rightleftharpoons H^+ + S^{2-}$ (2′)	Beauchamp et al. 1984; Budavari et al. 1996
pK_a (1')	7.04	
pK_a (2')	11.96	
Henry's law constant:		
at 20°C	468 atm/mole fraction	Al Haddad et al. 1989
at 30°C	600 atm/mole fraction	
at 40°C	729 atm/mole fraction	
Autoignition temperature	500°C	OHM/TADS 1998
Flammability limits	Upper, 46%; lower, 4.3% (by volume at room temperature)	
Conversion factors	1 ppm = 1.40 mg/m^3	NIOSH 1997
Explosive limits	Upper, 46%; lower 4.3% (by volume in air)	Budavari et al. 1996

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Hydrogen sulfide may be produced by a variety of different commercial methods including reacting dilute sulfuric acid with iron sulfide, heating hydrogen and sulfur into their vapor phases, and heating sulfur with paraffin (HSDB 1998). The principal source of hydrogen sulfide is recovery as a by-product in the purification of natural and refinery gases (Beauchamp et al. 1984). Another method of hydrogen sulfide recovery is hydrodesulfurization in which gas-oil and coke distillate fractions with high sulfur contents are passed through a fixed-bed catalyst in the presence of hydrogen (Beauchamp et al. 1984). This is done by absorbing the gas with monoethanolamine or diethanolamine (HSDB 1998).

Hydrogen sulfide is not listed in the Toxics Release Inventory as of October, 1998.

4.2 IMPORT/EXPORT

No data on import or export volumes for hydrogen sulfide are available.

4.3 USE

Hydrogen sulfide has a variety of industrial uses. Its major use is in the production of elemental sulfur and sulfuric acid. Hydrogen sulfide is also used in the manufacture of sodium sulfide and thiophenes. It is used in metallurgy and in the production of heavy water for the nuclear industry (Beauchamp et al. 1984; HSDB 1998). In the past, hydrogen sulfide was used as an agricultural disinfectant.

4.4 DISPOSAL

Hydrogen Sulfide is listed as a toxic substance under Section 3 13 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing hydrogen sulfide is controlled by a number of federal regulations (see Chapter 7).

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Hydrogen sulfide is considered to be a hazardous waste when discarded as a commercial chemical product, an off-specification commercial chemical product, or a manufacturing chemical intermediate (HSDB 1998). The EPA-assigned hazardous waste number for hydrogen sulfide is U135. Additional information concerning the accidental release of hydrogen sulfide and its reporting requirements is found in Chapter 7.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Hydrogen sulfide has been identified in at least 29 of the 1,467 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1998). However, the number of sites evaluated for hydrogen sulfide is not known. The frequency of these sites within the United States can be seen in Figure 5-l.

Hydrogen sulfide is produced naturally through nonspecific and anaerobic bacterial reduction of sulfates and sulfur containing organic compounds (Hill 1973). It is commonly emitted from stagnant **or** polluted waters and manure or coal pits with low oxygen content, and to a far lesser extent from volcanoes. These natural sources account for about 90% of the total hydrogen sulfide in the atmosphere (EPA 1993). It may enter the environment through accidental release, leakage during manufacture or use, or as a result of industrial waste disposal. Because hydrogen sulfide is a natural component of petroleum, sulfur, and natural gas deposits, it may also be released into the environment during the extraction, transport, and refining of these resources. Landfills may be a source of ambient hydrogen sulfide in the air (HazDat 1997).

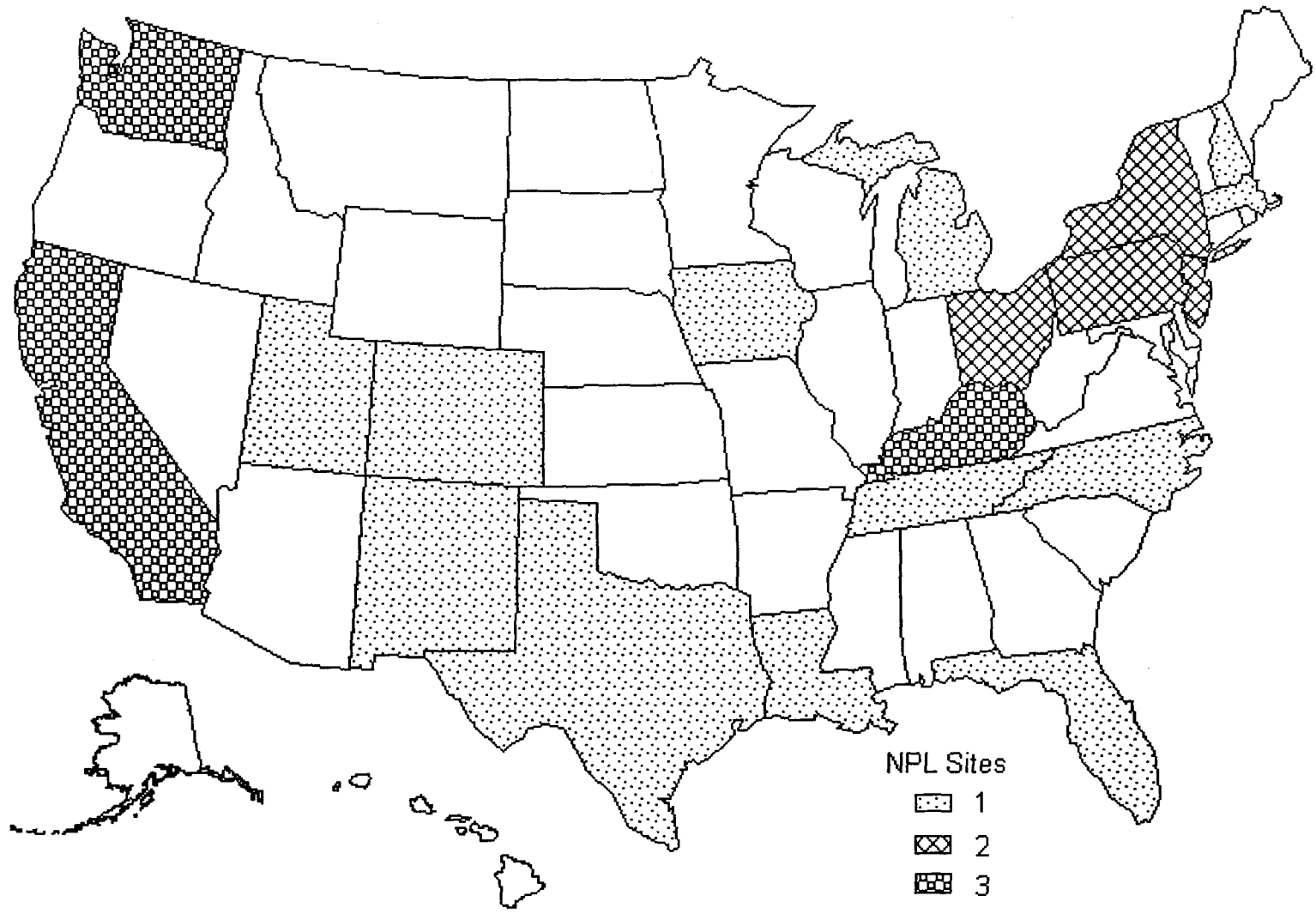
Hydrogen sulfide is readily soluble in water, which makes it highly mobile in moist soils and in aquatic and marine environments. It may also become sorbed onto clay or organic matter. Several species of soil, aquatic, and marine microorganisms oxidize hydrogen sulfide to elemental sulfur, and its half-life in these environments usually ranges from 1 hour to several hours (,Jorgensen 1982). Because it is a gas under ambient conditions, bioconcentration and food chain biomagnification are unlikely.

5.2 RELEASES TO THE ENVIRONMENT

Hydrogen sulfide is not listed in the Toxics Release Inventory as of October, 1998.

Hydrogen sulfide has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 29 of the 1,467 NPL hazardous waste sites (HazDat 1998).

Figure 5-1. Frequency of NPL Sites with Hydrogen Sulfide Contamination



*Derived fromHazDat 1998

5.2.1 Air

Hydrogen sulfide is produced naturally and as a result of human activity. Natural sources, such as swamps, bogs, and volcanoes, account for about 90% of the total amount of hydrogen sulfide in the atmosphere (EPA 1993). Many petroleum deposits and natural gas wells also contain hydrogen sulfide ("sour-gas wells") and become sources of atmospheric hydrogen sulfide release when developed (Layton and Cederwall 1986; Leahey and Schroeder 1986). Hydrogen sulfide is emitted by some plant species as a byproduct of sulfite metabolism (Takemoto et al. 1986; Wilson et al. 1978). Estimates of the terrestrial emission rate of hydrogen sulfide range from 58 to 110 million tons of sulfur/year (Hill 1973). Estimates of the emission rate from oceans range from 30 to 170 million tons of sulfur/year (Hill 1973).

Hydrogen sulfide is chemically synthesized for use in the manufacture of rayon textiles, as an agricultural disinfectant, and as an additive in lubricants and cutting oils (HSDB 1998; Tyagi et al. 1988). It is a byproduct of kraft pulp and paper manufacturing and is used as an intermediate in the manufacture of sulfuric acid and inorganic sulfides (HSDB 1998; Kauppinen et al. 1997; Tyagi et al. 1988). Accidental release or improper disposal of materials resulting from these processes may result in hydrogen sulfide emissions. Ambient hydrogen sulfide concentrations in the air near landfills indicate that they may be a source as well (HazDat 1997).

5.2.2 Water

Releases of hydrogen sulfide to water occur both naturally and as a result of human activity. Hydrogen sulfide released from aquatic plants, or as a result of anaerobic chemical processes in swamps and bogs, may dissolve in the water column or bind to clay or organic matter.

Hydrogen sulfide is chemically synthesized for use in the manufacture of rayon textiles, as an agricultural disinfectant, and as an additive in lubricants and cutting oils (HSDB 1998; Tyagi et al. 1988). It is a byproduct of kraft pulp and paper manufacturing and is used as an intermediate in the manufacture of sulfuric acid and inorganic sulfides (HSDB 1998; Tyagi et al. 1988). Gaseous plumes or waters that contain hydrogen sulfide may serve as contamination sources in receiving waters (EPA 1993).

5.2.3 Soil

Hydrogen sulfide may enter the soil through deposition from the atmosphere, mobilization through migrating pore water, or from leaks and spills during manufacture, transport, or storage. Hydrogen sulfide is readily soluble in water, which makes it highly mobile in moist soils.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Since hydrogen sulfide exists as a gas at atmospheric pressure, partitioning to the air is likely to occur after environmental releases. However, the compound is also soluble in oil and water, and therefore, may partition to surface waters, groundwaters, or moist soils, and subsequently travel great distances. In addition, sorption of hydrogen sulfide from air onto soils (Cihacek and Bremner 1993) and plant foliage (De Kok et al. 1983, 1988. 1991) may occur.

Hydrogen sulfide may evaporate easily from water, depending on factors such as temperature, humidity, and pH. In general, low pH and high temperature tend to favor evaporation (HSDB 1998). The Henry's Law constant was determined under a variety of conditions for hydrogen sulfide dissolved in sewage or distilled water and was found to increase linearly with temperature, indicating an increasing tendency to partition to the gas phase (Al-Haddad et al. 1989). Other factors found to increase the Henry's constant in sewage were pH, pK, flow rate, and initial hydrogen sulfide concentration.

Hydrogen sulfide transport in water occurs readily in moist soils and aquatic and marine environments because of its solubility. Hydrogen sulfide's solubility in pure water varies with temperature from 4 mL/mL at 4°C to 2.55 mL/mL at 20°C (Boon 1992). However, it may also become sorbed onto clay or organic matter. Several species of soil, aquatic, and marine microorganisms oxidize hydrogen sulfide to elemental sulfur, and its half-life in these environments usually ranges from 1 hour to several hours (Jorgensen 1982). Food chain bioconcentration and biomagnification are unlikely (HSDB 1998).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Hydrogen sulfide in the air is oxidized at a relatively slow rate by molecular oxygen (0,) but at a much faster rate by hydroxide (OH) radicals, forming the sulfhydryl radical and ultimately sulfur dioxide or sulfate compounds (Hill 1973; NSF 1976). Sulfur dioxide and sulfates are eventually removed from the atmosphere through absorption by plants and soils or through precipitation (Hill 1973).

Although hydrogen sulfide does not react photochemically, it may be transformed to sulfur dioxide and sulfate by nonphotochemical oxidation reactions in the atmosphere. Its atmospheric residence time is typically less than 1 day (Hill 1973), but may be as high as 42 days in winter (Bottenheim and Strausz 1980).

5.3.2.2 Water

Hydrogen sulfide oxidation by O_2 may readily occur in surface waters. Oxidation by H_2O_2 may also occur, primarily in rainwater and marine aerosols, where concentrations of H_2O_2 are relatively high (Millero et al. 1989). Hydrogen sulfide in waste water may be controlled by addition of oxidizing chemicals which react to form harmless byproducts (Tomar and Abdullah 1994). In warm, damp environments (such as manholes and gravity sewers), hydrogen sulfide may be oxidized by autotrophic bacteria to sulfuric acid (Boon 1992). Chemical oxidation of hydrogen sulfide dissolved in sewage water produces sulfur at pH 6-7, while sulfur, polysulfides, thiosulfates, and ultimately sulfate are formed at pHs of 7-9 (Boon 1992).

Hydrogen sulfide ionization in water may occur, dependent primarily upon pH. The predominant chemical form under typical environmental conditions is hydrogen sulfide, although the sulfhydryl radical (SH^-) becomes more abundant with increasing pH (Hill 1973). The first acid dissociation (pK_a) is 7.04. SH^- is generally thought to be the lesser toxicological hazard, as it is not as readily absorbed across biological membranes as hydrogen sulfide. However, some evidence suggests that SH^- may produce toxic effects in fish in hydrogen sulfide-contaminated water at higher pHs (Broderius et al. 1977).

5.3.2.3 Sediment and Soil

Soils may sorb considerable amounts of hydrogen sulfide from the air, retaining most of it in the form of elemental sulfur (Cihacek and Bremner 1993).

A number of microorganisms have been found to degrade hydrogen sulfide to elemental sulfur or sulfate. Among these are a heterotrophic bacterium of the genus *Xanthomonas* isolated from dimethyl disulfide-acclimated peat (Cho et al. 1992), heterotrophic fungi (Phae and Shoda 1991), and a marine isopod (Vismann 1991).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to hydrogen sulfide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on hydrogen sulfide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

Hydrogen sulfide ambient air concentrations from natural sources have been estimated to be between 0.15 and 0.46 µg/m^3 (0.11 and 0.33 ppb) (EPA 1993). In an unpolluted area of Colorado, concentrations between 0.03 and 0.1 µg/m^3 (0.02 and 0.07 ppb) were measured (Hill 1973). Near ground level, samples taken around a sulfurous New Zealand lake charged by an active underground geothermal vent had average hydrogen sulfide levels of 5-3,900 ppb, which produced no visible adverse effects on indigenous bird or plant populations (Siegel et al. 1986).

An air monitoring study at a waste-water treatment plant in Australia found time-averaged hydrogen sulfide levels of l-2 ppm near the primary clarifiers and inlet structure, and levels cl ppm at various other locations in the 10-hectare plant site (Koe 1985).

Hydrogen sulfide levels in air on some NPL sites ranged from 0.9 to 808 ppm (HazDat 1997). Data on ambient air concentrations at all NPL sites were not available, however.

5.4.2 Water

Hydrogen sulfide readily evaporates from surface waters and is not likely to persist in highly oxygenated waters; levels in these environments are expected to be low. Groundwater samples from an area receiving acid-mine drainage in Colorado averaged 0.9 ppm of hydrogen sulfide, while samples from a power plant site averaged 0.03 ppm (Patterson and Runnells 1992).

Accurate measurements of hydrogen sulfide water levels are usually complicated by the presence of other sulfide compounds. A method of determining sulfide concentration in waste water by first transforming it to hydrogen sulfide and then measuring the atomic absorption of the product yielded results ranging from 3.1 to 5.1 ppm of sulfide sulfur (Parvinen and Lajunen 1994). Total sulfide levels in samples from the Mississippi River were about 0.92 ppm, while levels in pond and well water in St. Paul, Minnesota were 1.6 and 1.9 ppm, respectively (Slooff et al. 1991).

5.4.3 Sediment and Soil

Levels as high as 11.7 ppm in soil solution were measured in Louisiana rice fields (Hollis 1985). The hydrogen sulfide in these samples was presumably bound to colloidal clay or organic matter, as these levels were higher than typical solubility would predict and were not accompanied by the characteristic hydrogen sulfide odor. Sediment pore water from the Grand Calumet River in an industrialized area of Indiana contained 0.2-l 5 ppb of hydrogen sulfide (Hoke et al. 1993). In general, undisturbed anoxic sediment pore water may contain up to 100 ppb hydrogen sulfide, while disturbed sediments typically contain pore water concentrations of l-30 ppb (Dillon et al. 1993).

Concentrations of hydrogen sulfide in soil gas from samples taken at some NPL sites ranged from 75 to 47,000 ppm (HazDat 1997). Data on soil gas concentrations at all NPL sites were not available.

5.4.4 Other Environmental Media

Hydrogen sulfide is commonly found in coal and petroleum deposits and may be mobilized by human manipulation of these resources. Coal gasification, a process whereby coal is subjected to heat and steam treatment to produce a convenient energy source, results in a gas product consisting of 0-1 % hydrogen sulfide (Barik et al. 1987).

5. POTENTIAL FOR HUMAN EXPOSURE

Hydrogen sulfide formation has been demonstrated in pediatric intravenous amino acid solutions used to treat infants with high protein requirements (Decsi and Koletzko 1993). Levels up to 1.96 ppm were found, presumably formed by sulfide liberation from cysteine derivatives during heat sterilization. Similar chemical reactions may explain the presence of hydrogen sulfide in dental plaque (Tonzetich and Carpenter 1971). Meat products may be contaminated with hydrogen sulfide-producing bacteria, resulting in off-odors and spoilage (McMeekin and Patterson 1975).

Hydrogen sulfide is produced in the large intestine of mammals by metabolism of sulfhydryl proteins by anaerobic bacteria. and may compose 0-10% of intestinal gases (Beauchamp et al. 1984; EPA 1978). It is produced in the human mouth by microbial petrification (Rosenberg et al. 1991).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to hydrogen sulfide by accidental release (“blowout”) from natural gas wells during drilling operations near residential areas (Layton and Cederwall 1986; Leahey and Schroeder 1986). Workers may be occupationally exposed to hazardous levels of hydrogen sulfide from fermenting manure (Morse et al. 198l), stagnant wells (McDonald and McIntosh 195l), as well as in poorly ventilated areas of waste-water treatment facilities (NIOSH 1980b, 1984, 1985a, 1985d, 1990), extruded rubber plants (NIOSH 1985b), and petroleum refineries (NIOSH 1982a, 1982b).

Toxic exposure data for 1995, compiled from 67 poison control centers, indicated that there were 1,407 (1,400 unintentional) hydrogen sulfide exposures during that year (Litovitz et al. 1996). None of these individuals died and the vast majority of these exposures resulted in outcomes that were either minor or nonexistent. Approximately 34% of the exposed individuals were treated in a health care facility (Litovitz et al. 1996).

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in 2.6 Children’s Susceptibility.

5. POTENTIAL FOR HUMAN EXPOSURE

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, they put things in their mouths, they may ingest inappropriate things such as dirt or paint chips, they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Hydrogen sulfide is found naturally in crude petroleum, natural gas, volcanic gases, hot springs, and often as the result of bacterial breakdown of organic matter. Children are more likely to be exposed near animal waste sites such as the sediments of fish aquaculture, livestock barns, or manure areas. Inhalation is the most likely source of exposure, and there are no known exposure pathways that are unique to children, although hydrogen sulfide is heavier than air so that children might be exposed to higher concentrations than adults. Children living in areas of geothermal activity, near waste sites or industries such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, and tanneries are more likely to be exposed. In a clinical case involving a 20-month-old child whose parents lived beside a coal mine where a burning tip had been emitting hydrogen sulfide for nearly 1 year, the patient had symptoms of ataxia and an abnormal CT scan of the brain (Gaitonde et al. 1987). Monitoring data showed that the hydrogen sulfide levels in the air were approximately 0.6 ppm but may have been higher before data were collected.

Hydrogen sulfide is also produced by bacteria in the mouth and gastrointestinal tract, as well as being found naturally in the brain where it may play a role in associative learning. In experimental studies in rats, the normal level in the brain was just half that found after a lethal exposure, suggesting a narrow margin of safety between requirement and toxicity (Warenycia et al. 1989a). Given that the blood brain barrier is not yet fully developed in infants, exposures early in life might be more likely to overwhelm this margin of safety (Adinolfi 1985).

Hydrogen sulfide formation has been demonstrated in pediatric intravenous amino acid solutions used to treat infants with high protein requirements (Decsi and Koletzko 1993). Levels up to 1.96 ppm were found, presumably formed by sulfide liberation from cysteine derivatives during heat sterilization.

Exposures have occurred through the mixing of acid and basic drain cleaners, and through the use of acid drain cleaner to remove sludge-clogged drains, but these incidents have been rare (Oderda 1975).
There are no known studies which hydrogen sulfide levels were measured in the blood or other tissues of children. It is not clear whether hydrogen sulfide can be transferred from mother to fetus although there is limited evidence that women occupationally exposed to hydrogen sulfide have a higher rate of spontaneous abortions (Hemminki and Niemi 1982; Xu et al. 1998).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers employed at facilities that manufacture or use hydrogen sulfide in the production process are especially prone to exposure. Such industries include the manufacture of rayon textiles, lubricants, pulp and paper, and sulfuric acid and inorganic sulfides. Workers in facilities where hydrogen sulfide is produced as a byproduct, such as farms with manure storage pits, petroleum or natural gas drilling operations, landfills, and waste-water treatment plants, may also be exposed to high levels.

5.8 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hydrogen sulfide is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrogen sulfide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.8.1 identification of Data Needs

Physical and Chemical Properties. Information is available on the physical and chemical properties of hydrogen sulfide (ACGIH 1991; Amoore and Hautala 1983; Budavari et al. 1996; HSDB 1998; Leonardos et al. 1969; Lide and Frederikse 1993; NIOSH 1997). However, additional information on those properties that determine the specific fate, transport, and rates of transformation of hydrogen sulfide as part of the larger sulfur cycle would be useful in discerning the environmental fate and behavior of this compound.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and ernissions. However, hydrogen sulfide is not required to be reported under the TRI.

Environmental Fate. Hydrogen sulfide is known to easily evaporate into the air (EPA 1993; Layton and Cederwall 1986; Leahey and Schroeder 1986), although its solubility in water may also cause it to persist in unperturbed, anoxic sediments. Additional information on the transport, transformation, and persistence of the compound in soils and groundwater, particularly at hazardous waste sites, would be useful in identifying the most important routes of human exposure to hydrogen sulfide.

Bioavailability from Environmental Media. Additional information on absorption following dermal contact with, or ingestion of, contaminated soil and water would also be helpful in determining the importance of this route of exposure for populations of concern.

Food Chain Bioaccumulation. Sufficient information is available to demonstrate that hydrogen sulfide is not likely to bioaccumulate or biomagnify in the food chain.

Exposure Levels in Environmental Media. Monitoring of hydrogen sulfide levels in ambient air is currently sporadic; additional, more systematic sampling is needed, particularly in areas that may have a significant source of hydrogen sulfide. Methods for accurately measuring dissolved sulfides in water are also available, although methods specific to hydrogen sulfide concentration are needed. Reliable monitoring data

for the levels of hydrogen sulfide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hydrogen sulfide in the environment can be used in combination with the known body burdens of hydrogen sulfide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. More data on the levels of hydrogen sulfide at the point of emission (on-site) versus levels at the point of exposure (off-site) are needed.

Exposure Levels in Humans. Occupational studies often do not report exposure levels. Additional information is needed on the exposure levels among populations living in the vicinity of hazardous waste sites and other potential sources of hydrogen sulfide, such as hot springs and waste water treatment plants.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children

The only information that provided an assessment of exposure of children and adolescents to hydrogen sulfide was that developed during the South Karelia Air Pollution Study (Mortilla et al. 1994b); however, these exposures were complicated by simultaneous exposure to other sulfur-containing compounds as well as particulates. Additional exposure information is needed from communities where only hydrogen sulfide exceeds background levels.

Exposure Registries. No exposure registries for hydrogen sulfide were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.8.2 Ongoing Studies

Much current research regarding the behavior of hydrogen sulfide in the environment involves developing methods to enhance biodegradation and transformation to less harmful products. A.A. Dispirito and D.L. Harris at Iowa State University are investigating the manipulation of culture conditions as a way to increase the efficiency of hydrogen sulfide degradation by fermentative microorganisms in lagoon systems used in the

storage of livestock wastes. The contribution of hydrogen sulfide to odor emissions from swine confinement facilities and effective methods for reducing exposure of workers is being studied by J.A. Pickrell and associates at Kansas State University. E.C. Clausen at Engineering Resources, Inc., Fayetteville, AR, is investigating the use of bacteria to produce elemental sulfur from the excess hydrogen sulfide produced by natural gas drilling. Other studies on removing hydrogen sulfide from petroleum reserves are being conducted by R. Ray and D.J. Edlund at Bend Research, Inc., Bend, OR; R.L. Goldsmith at CeraMem Corporation, Waltham, MA; M.E. Karpuk and R.J. Copeland at TDA Research, Wheat Ridge, CO; S.R. Robinson at Oaks Travel, Inc., Houston, TX; J. Winnick at the Georgia Institute of Technology, Atlanta, GA; and S.K. Gangwal at the Research Triangle Institute, Research Triangle Park, NC. The effects of hydrogen sulfide on marine copepod eggs are being studied by N.H. Marcus at Florida State University, Tallahassee, FL. Research on the contribution of hydrogen sulfide and other volcanic emission gases to the global sulfur cycle is being performed by J.A. Crisp at the California Institute of Technology, Pasadena, CA.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring hydrogen sulfide, its metabolites, and other biomarkers of exposure and effect to hydrogen sulfide. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

A limited number of analytical techniques have been used for measuring hydrogen sulfide in the breath (expired air) and biological tissues and fluids including blood and saliva. These include gas chromatography coupled with flame ionization detection (GC/FID), gas chromatography coupled with flame photometric detection (GC/FPD), iodometric titration, potentiometry with ion-selective electrodes, spectrophotometry, and high-performance liquid chromatography (HPLC). Details of commonly used analytical methods for several types of biological media are presented in Table 6- 1.

Puacz et al. (1995) developed a catalytic method, based on the iodine-azide reaction, for the determination of hydrogen sulfide in human whole blood. The method involves the generation of hydrogen sulfide in an evolution-absorption apparatus. In addition, the method allows for the determination of sulfide in blood without interference from other sulfur compounds in blood. A detection limit of 4 μg /dm^3 and a percent recovery of 98-102% were achieved. Although the accuracy and precision of the catalytic method are comparable to those of the ion-selective electrode method, the catalytic method is simpler, faster, and would be advantageous in serial analysis.

GC/FPD was employed for measuring hydrogen sulfide in human breath with a detection sensitivity capable of 7 ppb (Blanchette and Cooper 1976) and included improvements such as calibration of the system with

TABLE 6-1. Analytical Methods for Determining Hydrogen Sulfide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	React iodine with sodium azide at pH 6.5–6.8 in the presence of diluted whole human blood.	Iodometric method	4 μg/dm^{-3}	98–102	Puacz et al. 1995
	Add sulphide antioxidation reducing buffer to sample of whole blood.	Potentiometry (ion-selective electrode)		102	Puacz et al. 1995
	Add sulfuric acid to sample using wash-bottle reactor assembly; hydrogen sulfide carried by nitrogen flow into a vessel containing NaOH.	Ion-selective electrode	10 μg/L	NR	Lindell et al. 1988
Blood and Urine	For thiosulfate detection, add 0.2 ml sample to mixture of 0.5 ml of 20 mM pentafluoro-benzyl bromide (PFBBr) solution in acetone, 0.05 ml of 200 mM L-ascorbic acid solution and 0.05 ml of 5% sodium chloride. Vortex for 1 minute and add 2 ml of 25 mM iodine solution in ethyl acetate and 0.5 ml of internal standard solution (40 μM 1,3,5 tribromobenzene (TBB) in ethyl acetate). Vortex 30 seconds and centrifuge at 2,500 rpm for 15 minutes, allow to stand for 1 hour.	GC-ECD	3 nmol/mL	NS	Kage et al. 1997

TABLE 6-1. Analytical Methods for Determining Hydrogen Sulfide in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood and Urine	For sulfide detection, add 0.2 mL of sample to mixture of 0.5 mL of 20 mM PFBBr solution in toluene, 2.0 mL of internal standard solution (10 µM TBB in ethyl acetate) and 0.8 mL of 5 mM tetradecyldimethylbenzyl-amomonium chloride solution in oxygen-free water saturated with sodium tetraborate. Vortex 1 minute, add 0.1 g potassium dihydrogenphosphate as a buffer. Vortex for 10 seconds, centrifuge at 2,500 rpm for 10 minutes.	GC-ECD	0.3 nmol/mL	NS	Kage et al. 1997
Urine	Freeze and store freshly voided urine samples at -25 C until analysis within 24 hours after exposure. Analyze urinary thiosulfate as its bromobimane product. Correct results for the excreted creatinine analyzed in the same samples.	Liquid Chromatography	50 µmol/L; 20 µmol/L	92; 80	Kangas & Savolainen 1987

TABLE 6-1. Analytical Methods for Determining Hydrogen Sulfide in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath	Connect Teflon sampling probe to analyzer and syringe through a sampling valve and loop; insert probe 4 cm into mouth between closed lips; withdraw 20 mL over 6 seconds into syringe; flush and fill the sample loop with 10 mL mouth air; carry sample to analysis in nitrogen gas.	GC/FID	7 ppb	NR	Blanchette and Cooper 1976
Breath	Collect air from breathing zone using a midget impinger containing calcium hydroxide-calcium sulfide-arabinogalactan slurry; add solution of *N,N*-dimethyl-*p*-phenylenediamine and ferric chloride.	Spectrophotometry	0.20 $\mu g/m^3$	80	NIOSH 1977
Saliva	Collect 3 mL aliquot with sterile pipette; introduce into 2-ounce glass container and cap; incubate 24 hours at 37°C; withdraw through cap with gas-tight syringe.	GC/FID, microcoulometric tritration	NR	NR	Solis and Volpe 1973

TABLE 6-1. Analytical Methods for Determining Hydrogen Sulfide in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Tissue	Weigh sample; homogenize in aqueous zinc acetate using a rotostator at 18,000 rpm for 20 seconds; dilute with borate buffer; convert to methylene blue.	Ion-interaction reversed-phase HPLC	nmol g^{-1}	NR	Mitchell et al. 1993
Brain tissue	Homogenization in coid 0.01 M NaOH. Centrifuge and resuspend pellet; add zinc acetate and ascorbic acid; readjust pH; use continuous flow gas dialysis system to separate sulfide.	Gas dialysis/ion chromatography with ECD	0.02 µg/g	95–100%	Goodwin et al. 1989

ECD = electrochemical detection; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; M = molar; NaOH = sodium hydroxide; NR = not reported; rpm = revolutions per minute

permeation tubes, use of a variable beam splitter to produce a wide range of vapor concentrations, and the ability to handle samples of limited volume.

For occupational measurements of airborne concentrations, NIOSH (1977aj recommended the use of a midget impinger for sampling breathing zone air and the methylene blue/spectrophotometric method for the analysis of hydrogen sulfide. The detection limit was 0.20 μg/m^3 (0.14 ppb).

GC/FID has been used for quantifying sulfur volatiles such as hydrogen sulfide in human saliva (Solis and Volpe 1973). This method included microcoulometric titrations and a procedure for incubation of saliva and sampling of headspace sulfur volatile components. The amount of total sulfur volatiles detected in control samples of saliva incubated at 37°C for 24 hours ranged from 4.55 to 13.13 ppm.

Fresh and frozen human tissue samples obtained from brain, liver, and kidney have been analyzed for hydrogen sulfide levels by sulfide-derived methylene blue determination using ion-interaction reversed-phase HPLC (Mitchell et al. 1993). This method can quantify nmol/g levels of sulfide. Gas dialysis/ion chromatography with ECD has been utilized for measurement of sulfide in brain tissue with 95- 100% recovery (Goodwin et al. 1989).

6.2 ENVIRONMENTAL SAMPLES

The methods most commonly used to detect hydrogen sulfide in environmental samples include GC/FPD, gas chromatography with electrochemical detection (GC/ECDj, iodometric methods, the methylene blue calorimetric or spectrophotometric method, the spot method using paper or tiles impregnated with lead acetate or mercuric chloride, ion chromatography with conductivity, and potentiometric titration with a sulfide ion-selective electrode. Details of commonly used analytical methods for several types of environmental samples are presented in Table 6-2.

Several methods for determining hydrogen sulfide in air have been investigated. GC/FPD has been widely used for analyses of hydrogen sulfide at levels ranging from 10^{-11} to 10^{-8} grams/0.56 mL (EPA 1978; Stetter et al. 1977). Sampling of a standard reference (0.055 ppm hydrogen sulfide) with this method resulted in a relative standard deviation of <3% (WHO 1981). The sensitivity of hydrogen sulfide detection in air was improved with GC/ECD (Stetter et al. 1977). The detector operation is based upon the measurement of the current when hydrogen sulfide is electrochemically oxidized at a diffusion electrode. Use of this method

TABLE 6-2. Analytical Methods for Determining Hydrogen Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Filter through a 0.5-µm Zefluor; absorb on a solid sorbent tube containing coconut shell charcoal; desorb with ammonia hydroxide and hydrogen peroxide; dilute.	Ion chromatography and conductivity	11 µg/sample; working range 0.6–14 ppm for a 20-L air sample	NR	NIOSH 1994b (method 6013)
	Aspirate through cadmium hydroxide; precipitate as cadmium sulfide; add STRactan 10®; react with *N,N*-dimethyl-*p*-phenylenediamine and ferric chloride to yield methylene blue.	Spectrophotometry	0.20 µg/m^3	80	Anonymous 1975; EPA 1978; NIOSH 1977
	Aspirate through sodium hydroxide and ethanol; react with *N,N*-dimethyl-*p*-phenylenediamine and ferric chloride to yield methylene blue.	Spectrophotometry	No data	NR	Van Den Berge et al. 1985
	Absorb onto cadmium(II)-exchange zeolite; precipitate as cadmium sulfide; convert to methylene blue; measure at 750 nm.	PAS	0.01 µg	NR	Mark 1979
	Electrochemically oxidize sample at potential-controlled Teflon-bonded diffusion electrode.	GC/ECD	3 pg	NR	Stetter et al. 1977
	Introduce sampled air and carrier gas onto column.	GC/FPD	5–13 µg/m^3	NR	EPA 1978
	Introduce sample onto column packed with activated carbon fiber.	GC/FPD	No data	NR	Choi et al. 1991

TABLE 6-2. Analytical Methods for Determining Hydrogen Sulfide in Environmental Samples (*continued*)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
	Absorb in an impinger containing a standardized solution of iodine and potassium iodide; titrate with standard sodium thiosulfate solution.	Iodometric titration	No data	NR	EPA 1978
	Trap H_2S in an aqueous NaOH and ascorbic acid in a midget impinger; titrate resulting sulfide ion with $CdSO_4$ solution.	Potentiometry	ppb levels	NR	Ehman 1976
	Aspirate through ammoniacal cadmium chloride; strip sulfur dioxide by aeration; dissolve cadmium sulfide; precipitate in concentrated HCl; titrate with iodine using a starch indicator.	Iodometric titration	0.7 µg/L	NR	EPA 1978
	Filter measured volume of air through lead-acetate-impregnated filter paper tape; compare optical density with unexposed impregnated spot of similar area.	Lead-acetate-impregnated filter paper tape	No data	NR	EPA 1978
	Filter measured volume of air through mercuric chloride impregnated filter paper tape; compare optical density with unexposed impregnated spot of similar area.	Mercuric chloride–impregnated filter paper tape	0.7 µg/m^3	NR	EPA 1978
	Pass air through silver membrane filter.	Silver membrane filters/ optical density measurements	No data	NR	EPA 1978

TABLE 6-2. Analytical Methods for Determining Hydrogen Sulfide in Environmental Samples (*continued*)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment	Trap hydrogen sulfide in sodium hydroxide; sulfide reacts with *N,N*-dimethyl-*p*-phenylene-diamine to form methylene blue.	Colorimetry	0.01 µmol/gram	NR	Allen et al. 1994
Sediment	Trap in silver nitrate.	Gravimetry	10 µmol/g	NR	Allen et al. 1994
Sediment	Trap in silver nitrate.	Potentiometry/ ion-selective electrode	No data	NR	Allen et al. 1994
Water	Collect water sample; acidify; strip sample with helium; collect gas in nitrogen-cooled trap.	GC/FPD	0.6 pmol/L	NR	Radford-Knoery and Cutter 1993
Water and sludge	Acidify sample; measure absorption at 196.0 nm using the selenium atomic line.	AAS	0.25 µg	NR	Parvinen and Lajunen 1994

AAS = atomic absorption spectroscopy; $CdSO_4$ = cadmium sulfate; GC/ECD = electrochemical gas chromatographic detection; GC/FPD = gas chromatography with flame photometric detection; HCl = hydrochloric acid; H_2S = hydrogen sulfide; NaOH = sodium hydroxide; NR = not reported; PAS = photoacoustic spectroscopy

resulted in a lower detection limit of $3x10^{-12}$ grams hydrogen sulfide and a precision of 0.5%. Analyses were achieved within 2 minutes. GC/FPD has been used to measure hydrogen sulfide that has been removed from air by activated carbon fibre (Choi et al. 1991). Activated carbon fibre, made from coal tar, effectively oxidized hydrogen sulfide (200 ppm) to sulfate.

Methylene blue techniques have been widely utilized for continuous, quantitative monitoring of hydrogen sulfide in air and are sensitive to hydrogen sulfide concentrations as low as approximately 0.001-0.003 ppm (NIOSH 1977a). This method provides adequate specificity with good accuracy and precision (WHO 1981). The amount of sulfide is determined by spectrophotometric or calorimetric measurement of methylene blue. The method has been improved to eliminate the formation of the precipitate cadmium sulfide which can result in the obstruction of the sampling impinger (Van Den Berge et al. 1985). Also, the simplified method can be used to measure hydrogen sulfide levels in the viscose rayon industry because it is not as sensitive to carbon disulfide. A limitation of the methylene blue method is potential interference from light, mercaptans, sulfides, nitrogen dioxide, and sulfur dioxide (NIOSH 1977a). Photoacoustic spectroscopy of hydrogen sulfide converted to methylene blue has been demonstrated to yield greater sensitivity than standard spectrophotometric methods (NIOSH 1979). By maximizing instrument response to the 750-nm peak, it was possible to achieve a detection limit of 0.01 µg when collected at 2.0 L/minute for a l-hour period.

NIOSH (method 6013) describes the measurement of hydrogen sulfide in the air by ion chromatography (NIOSH 1994b). This method has a working range of 0.9-20 mg/m^3 for a 20-L air sample and an estimated limit of detection of 11 µg per sample. However, sulfur dioxide may interfere with the measurement of hydrogen sulfide.

The Iodometric method has also been utilized in analyzing hydrogen sulfide in the air (EPA 1978). The method is based on the oxidation of hydrogen sulfide by absorption of the gas sample in an impinger containing a standardized solution of iodine and potassium iodide. This solution will also oxidize sulfur dioxide. The Iodometric method is suitable for occupational settings. The accuracy of the method is approximately 0.50 ppm hydrogen sulfide for a 30-L air sample (EPA 1978).

Paper tapes impregnated with lead acetate have been widely used for air sample measurements of hydrogen sulfide in the field (EPA 1978; WHO 1981). The presence of other substances capable of oxidizing lead sulfide can lead to errors. This method has been improved by impregnating the paper with mercuric chloride or silver nitrate (EPA 1978; WHO 1981). Mercuric chloride paper tape is sensitive and reliable for

measurement of hydrogen sulfide in air with a sensitivity of 0.7 µg/L (EPA 1978). Tapes impregnated with silver nitrate are suitable for determination of hydrogen sulfide concentrations in the range of 0.001-50 ppm (WHO 1981).

Potentiometric titration with a sulfide ion-selective electrode as an indicator has been used to measure hydrogen sulfide in the air at ppb levels (Ehman 1976). The method has been shown to have very good accuracy and precision. No interference could be found from nitrogen dioxide, sulfur dioxide, or ozone.

Three methods for quantifying acid volatile sulfides in sediment have been described (Allen et al. 1994). These include methylene bluekolorimetric methods, gravimetry, and potentiometry with ion-selective electrode. Prior to measurement, the acid volatile sulfide in the sample is converted to hydrogen sulfide by acidification. The hydrogen sulfide is then purged from the sample and trapped in aqueous solution. The methylene bluekolorimetric method is generally preferred and is capable of determining acid volatile sulfide concentrations as low as 0.01 pmoles/gram dry weight of sediment. The gravimetric method can be used for samples with moderate or high acid volatile sulfides. However, below 10 µmoles acid volatile sulfides/gram dry sediment, accuracy may be affected by incomplete recovery of precipitate or by weighing errors. The limit of detection of the ion-selective electrode method as applied to measuring hydrogen disulfide in sediment was not reported.

GC/FPD has been used to measure hydrogen sulfide, free disulfide, and dissolved metal sulfide complexes in water (Radford-Knoery and Cutter 1993). Hydrogen sulfide was measured in the headspace of the sample (100 mL) with a detection limit of 0.6 pmol/L. A detection limit of 0.2 pmol/L was obtained for total dissolved sulfide. This method allows for the determination of the concentration of free sulfide that is in equilibrium with hydrogen sulfide. Complexed sulfide can be estimated from the difference between total dissolved sulfide and free sulfide.

A molecular absorption spectrophotometry method, using a sharp-line irradiation source, has been developed for the determination of sulfide (as hydrogen sulfide) in water and sludge samples. The method was tested with measurements of real waste-water samples, The limit of detection was 0.25 µg (l-10 mL sample volume).

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hydrogen sulfide is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrogen sulfide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for measuring hydrogen sulfide in expired air (Blanchette and Cooper 1976; NIOSH 1977a); blood (Puacz et al. 1995); saliva (Solis and Volpe 1973); and brain, liver, and kidney tissue (Mitchell et al. 1993). Available methods are accurate and reliable for most media. Although available methods can detect and quantify background levels of hydrogen sulfide in the population, there is no current ability to quantitatively correlate levels in blood or other tissues with environmental exposure levels, therefore, methods are needed that *can* quantitatively correlate levels in blood and other tissues with environmental exposure levels.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for measuring hydrogen sulfide in air (Ehman 1976; EPA 1978; NIOSH 1977, 1979, 1994b; Stetter et al. 1977; Van Den Berge et al. 1985; WHO 1981), sediment (Allen et al. 1994), water (Radford-Knoery and Cutter 1993), and sludge (Parvinen and Lajunen 1994). One difficulty in measuring environmental levels of sulfide compounds is distinguishing hydrogen sulfide from other sulfide species. Accurate methods that are specific to hydrogen sulfide and which minimize interference from other sulfide species are needed.

6.3.2 Ongoing Studies

Under a cooperative agreement with ATSDR, Texas Tech University is field testing the liquid wave guide technology using a novel fluoropolymer air sampling device (Dasgupta et al. 1998) to monitor hydrogen sulfide exposures at sites.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding hydrogen sulfide in air, water, and other media are summarized in Table 7-l.

Based on a LOAEL of 2 ppm for respiratory effects-bronchial obstruction (30% change in airway resistance) in 2/10 persons with asthma in the Jappinen et al. (1990) study, an acute inhalation MRL of 0.07 ppm was derived. An uncertainty factor of 30 was applied to the LOAEL; 10 for the use of a LOAEL and 3 for human variability. Since persons with severe asthma were excluded from the study, an uncertainty factor of 3 is needed to protect all sensitive individuals including children. Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile. Based on a NOAEL of 30.5 ppm for respiratory effects in mice observed in the CIIT (1983a) study, an intermediated MRL of 0.03 ppm was derived. The NOAEL is adjusted for intermittent exposure and the $NOAEL_{[HEC]}$ is calculated. An uncertainty factor of 30 is then applied; 3 for extrapolating from animals to humans and 10 for human variability. Further details on this MRL can be found in the MRL worksheets in Appendix A of this profile.

EPA has derived both an oral reference dose (RfD) and an inhalation reference concentration (RfC) for chronic exposure to hydrogen sulfide. The RfD of 0.003 mg/kg/day is based on the NOAEL of 3.1 mg/kg/day for gastrointestinal disturbance in pigs in a study by Wetterau et al. (1964) (IRIS 1998). The NOAEL value of 3.1 mg/kg/day was divided by an uncertainty factor of 1,000 to account for interspecies extrapolation (10), sensitive individuals (10), and subchronic exposure (10) (IRIS 1998). The RfC of 0.001 mg/ $m^3$is based on the $NOAEL_{[HEC]}$ of 1.01 mg/m^3 for inflammation of the nasal mucosa in $B6C3F_1$ mice (CIIT 1983a). The $NOAEL_{[HEC]}$ value of 1.01 mg/m^3 was divided by an uncertainty factor of 1,000 to account for sensitive individuals (10), subchronic exposure (10), and interspecies extrapolation (10) (IRIS 1998).

There are a number of regulations and guidelines for the use of hydrogen sulfide in occupational settings. OSHA has established an acceptable ceiling concentration of 20 ppm for hydrogen sulfide in the workplace, with a maximum level of 50 ppm allowed for a 10 minute maximum duration (OSHA 1998c). NIOSH has not established a recommended exposure limit for a time-weighted average, but it does recommend a ceiling limit of 10 ppm over a 10-minute period (NIOSH 1997). The American Conference of Governmental

TABLE 7-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	References
INTERNATIONAL			
WHO	Guideline value for drinking water is not detectable by consumers	No	WHO 1984
IARC	Cancer classification	No	IARC 1998
NATIONAL			
Regulations:			
a. Air:			
EPA	Administrative stay of toxic chemical release reporting requirements	Yes	EPA 1994a (59 FR 43048)
	Regulated Toxic Subtance	Yes	EPA 1998e (40 CFR 68.130)
	Threshold quantity for accidental release prevention	10,000 pounds	EPA 1998e (40 CFR 68.130)
OSHA	PEL–8-hour time weighted average	None	OSHA 1998c (29 CFR *1910.1000* Table Z-2)
	PEL–Acceptable Ceiling Concentration	20 ppm	OSHA 1998c (29 CFR *1910.1000* Table Z-2)
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift	50 ppm; 10 minutes, once only if no other measureable exposure occurs (maximum duration)	OSHA 1998c (29 CFR *1910.1000* Table Z-2)
	Toxic and reactive highly hazardous chemical which presents a potential for a catastrophic event at or above the threshold quantity	1,500 pounds	OSHA 1998a (29 CFR 1910.119 Appendix A)
	TLV of Airborne Contaminants for Construction	10 ppm; 15 mg/m^3	OSHA 1998b (29 CFR 1926.55 Appendix A)
b. Water:			
EPA	Hazardous substance under the Federal Water Pollution Control Act, Sec. 311(b)(2)(A)	Yes	EPA 1998f (40 CFR 116.4)
	MCL	None	EPA 1996
	MCLG	None	EPA 1996

TABLE 7-1. Regulations and Guidelines Applicable to Hydrogen Sulfide (*continued*)

Agency	Description	Information	References
NATIONAL			
	1-Day Health Advisory (child and adult)	None	EPA 1996
	10-Day Health Advisory (child and adult)	None	EPA 1996
	Longer Term Health Advisory	None	EPA 1996
	Lifetime Health Advisory	None	EPA 1996
c. Other:			
EPA OSW	Listing as a Hazardous Waste: Discarded commercial chemical products off-specification species, container residues, and spill residues thereof	Yes	EPA 1998d (40 CFR 261.33)
EPA CERCLA	Listed as a Hazardous Substance	Yes	EPA 1998c (40 CFR 302.4 Appendix A)
EPA	List of Extremely Hazardous Substances	Yes	EPA 1998b (40 CFR 355 Appendix A)
	Reportable Quantity	Category B (100 pounds)	EPA 1998c (40 CFR 302.4 Appendix A)
	Threshold Planning Quantity	500 pounds	EPA 1998b (40 CFR 355 Appendix A)
OSHA	Threshold Quantity for Toxic and Reactive Highly Hazardous Chemicals	1500 pounds	OSHA 1998a (29 CFR 1910.119 Appendix A)
Guidelines:			
a. Air:			
ACGIH	TLV-TWA	10 ppm; 14 mg/m^3	ACGIH 1998
	TLV-STEL	15 ppm	
AIHA	Emergency Response Planning Guidelines (ERPGs)		AIHA 1991
	ERPG-1	0.1 ppm	
	ERPG-2	30 ppm	
	ERPG-3	100 ppm	
NAS	24-hour EEGL	10 ppm	
	90-day CEGL	1 ppm	
NIOSH	REL (ceiling)	10 ppm; (15 mg/m^3) ceiling (10 minutes)	NIOSH 1997
b. Nonspecific media			
EPA	Oral RfD	3×10^{-3} mg/kg/day	IRIS 1998
	RfC	1×10^{-3} mg/m^3	IRIS 1998

TABLE 7-1. Regulations and Guidelines Applicable to Hydrogen Sulfide (*continued*)

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable Ambient Air Concentrations		
California	1-hour	3.0×10^{-2} ppm	CA Air Res Board 1998
Colorado	1-hour	1.42 $\mu g/m^3$	CO Air Poll Control Div 1998
Delaware	3-minute	6.0×10^{-2} $\mu g/m^3$	DE Air Quality Mgmt Sect. 1998
	1-hour	3.0×10^{-2} ppm	
Hawaii	1-hour	3.5×10^{1} $\mu g/m^3$	HI Environ Health Services Div 1998
Kentucky	1-hour	1.4×10^{1} $\mu g/m^3$	KY Div Air Quality 1998
Louisiana	8-hour	3.3×10^{2} $\mu g/m^3$	LA Air Qual Div 1998
Maryland	24-hour	3.79 $\mu g/m^3$	MD Air and Radiation Mgmt 1998
Massachusetts	24-hour	3.79 $\mu g/m^3$	MA Div Air Quality Control 1998
	Annual	3.79 $\mu g/m^3$	
Minnesota	30-minute, not to exceed 2 times/year	7.0×10^{1} $\mu g/m^3$	MN Div Air Quality 1998
	30-minute, not to exceed 2 times/5 days	4.2×10^{1} $\mu g/m^3$	
Missouri	30-minute, not to exceed 2 times/year	7.0x10-1 $\mu g/m^3$	MN Div Air Quality 1998
	30-minute, not to exceed 2 times/5 days	4.2×10^{1} $\mu g/m^3$	
Montana	1-hour	5.0×10^{-2} ppm (7.0×10^{1} $\mu g/m^3$)	MT Air Quality Division 1998
Nevada	8-hour	3.33×10^{-1} $\mu g/m^3$	NV Bureau Air Qual 1998
New Hampshire	ceiling	4.67×10^{2} $\mu g/m^3$	NH Air Resources Div 1998
New Mexico	1-hour	1.0×10^{-2} ppm	NM Air Qual Bur 1998
New Mexico (Pecos-Permian Basin)	30-minute	1.0×10^{-1} ppm	
New York	ceiling	1.4×10^{1} $\mu g/m^3$	NY Div Air Resources 1998
North Dakota	ceiling	1.4×10^{1} $\mu g/m^3$	ND Environ Health Sect 1998
	1-hour	2.8×10^{2} $\mu g/m^3$	
	24-hour	1.4×10^{2} $\mu g/m^3$	
Oklahoma	3-minute	1.0×10^{-1} ppm	OK Air Quality Div 1998
Pennsylvania	24-hour	5.0×10^{-3} ppm	PA Bureau Air Quality 1998

TABLE 7-1. Regulations and Guidelines Applicable to Hydrogen Sulfide (*continued*)

Agency	Description	Information	References
STATE (continued)			
Rhode Island	ceiling	1.4×10^{2} µg/m^3	RI Div Air Resources 1998
South Carolina	24-hour	1.4×10^{2} µg/m^3	SC Bureau Air Qual 1998
Texas	24-hour	9.0×10^{-1} µg/m^3	TX Nat Resource Conservation Comm 1998
Vermont	24-hour	3.33×10^{1} µg/m^3	VT Air Pollution Control 1998
Washington	24-hour	9.0×10^{-1} µg/m^3	WA Air Quality Prog 1998
Wyoming	30-minute, not to exceed 2 times/year	7.0×10^{1} µg/m^3	WY Air Quality Div 1998
	30-minute, not to exceed 2 times/5 days	4.0×10^{1} µg/m^3	

ACGIH = American Conference of Governmental Industrial Hygienists; AIHA = American Industrial Hygiene Association; CEGL = continuous exposure guidance level; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; EEGL = emergency exposure guidance level; EPA = Environmental Protection Agency; ERPG = Emergency Response Planning Guidelines; FR = Federal Register; IARC = International Agency for Research on Cancer; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NAS = National Academy of Sciences; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; PEL = personal exposure limit; REL = Recommended Exposure Limit; RfC = reference concentration; RfD = reference dose; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WQCAQ = Water Quality Criteria Aquatic Organisms; WHO = World Health Organization

7. REGULATIONS AND ADVISORIES

Industrial Hygienists (ACGIH) has established a threshold limit value, time-weighted average of 10 ppm (ACGIH 1998). Refer to Table 7- 1 for a more complete listing.

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9. GLOSSARY

Acute Exposure -Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coeffkient (**K_{oc}**)-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory- A n estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (**IDLH**)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro--Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo-Occurring within the living organism.

Lethal Concentration $_{(10)}$ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of lime is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(10)}$ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (**PEL**)-An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Reference Dose (**RfD**)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfIls are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (**RQ**)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (**STEL**)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (**TLV)**-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (**TWA**)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (**TD_{50}**)-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (**UF**)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (l-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Hydrogen sulfide
CAS Number:	7783-06-4
Date:	March 1999
Profile Status:	Draft 3 Post-Public
Route:	[x] Inhalation [ ] Oral
Duration:	[x] Acute [ ] Intermediate [ ] Chronic
Graph Key:	12
Species:	Human

Minimal Risk Level: 0.07 [ ] mg/kg/day [xl ppm

Reference: Jappinen et al. 1990

Experimental design:

This study evaluated the effect on pulmonary function in 10 asthmatic individuals (7 women and 3 men) who were exposed to 2 ppm hydrogen sulfide for 30 minutes.

Effects noted in study and corresponding doses:

Although no significant changes were noted in airway resistance (Raw) or specific airway conductance (SGaw), 2 of 10 subjects showed changes in excess of 30% in both Raw and SGaw, an indication of bronchial obstruction. These individuals showed no statistically significant changes in forced vital capacity, forced expiratory volume in 1 second, or forced expiratory flow; however 3 of 10 individuals reported headaches.

Dose and endpoint used for MRL derivation:

[ ] NOAEL [X] LOAEL

At 2 ppm 2 of 10 individuals with asthma showed changes in Raw and SGaw in excess of 30%.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 3 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
None

If an inhalation study in animals. list the conversion factors used in determining human equivalent dose:
None

Other additional studies or uertinent information which lend support to this MRL:

Bhambhani et al. (1996b) evaluated the acute effects of hydrogen sulfide on the physiological and hematological health of male and female volunteers exposed to 5 ppm during two 30-minute sessions of submaximal exercise (50% of maximum aerobic power). No significant changes in any parameter were noted in the women, whereas the men showed a significant decrease in muscle citrate synthetase as well as non-significant changes in lactate, lactate dehydrogenase, and cytochome oxidase. Together these changes were considered indicative of compromise of aerobic metabolism.

No respiratory or cardiovascular effects were observed in 16 male volunteers exposed to hydrogen sulfide at 0.5,2, or 5 ppm for more than 16 minutes while exercising (Bhambhani and Singh 1991). The end points examined included heart rate, oxygen uptake, carbon dioxide output, and blood gases. Airway resistance and conductance were not measured in this study. No significant changes in pulmonary function parameters were noted in individuals exposed to 10 ppm hydrogen sulfide for 15 minutes during exercise (Bhambhani et al. 1996).

Respiratory distress was noted in 2 workers exposed to greater than 40 ppm hydrogen sulfide for under 25 minutes (Spolyar 1951). In animals, impacts on the respiratory system such as increases in the cellularity and lactate dehydrogenase and alkaline phosphatase activities of bronchial lavage fluids have been seen at exposures as low as 10 ppm for 4 hours (Lopez et al. 1987) although without a dose-related trend.

A significant dose-related decrease in lung microsomal cytochrome c oxidase activity was seen in rats following a 4 hour exposure to 50,200, or 400 ppm hydrogen sulfide (Khan et al. 1990). Similarly, succinate oxidase activity also decreased in a dose-related fashion; although no affect was observed at the lowest dose. Cytochrome oxidase levels returned to normal by 24 hours post exposure in animals in the 200 ppm group, but not the 400 ppm group. Exposure at the two higher dose levels was also associated with complete abolition of the zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages and there were significant decreases in the number of viable macrophages in lung lavage fluids at the highest dose (Khan et al. 1991). Rats exposed to much higher levels (375 or 399 ppm for 4 hours) developed moderate to massive pulmonary edema (Prior et al. 1990).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Hydrogen sulfide
CAS Number:	7783-06-4
Date:	December 1998
Profile Status:	Draft 3 Post-Public
Route:	[x] Inhalation [ ] Oral
Duration:	[ ] Acute [x] Intermediate [ ] Chronic
Graph Key:	39
Species:	B6C3F1 Mice

Minimal Risk Level: 0.03 [ ] mg/kg/day [xl ppm

Reference: CIIT 1983a

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Ten male and 12 female B6C3F1 mice were exposed in exposure chambers 6 hr/day, 5 days/week for 90 days to time-weighted concentrations of 0, 10.1, 30.5 or 80.0 ppm hydrogen sulfide. Animals were sacrificed on study days 91-100 and were exposed up to the study day preceding sacrifice. Before necropsy, neurological function was analyzed by assessing posture, gate, tone of facial muscles, and pupillary reflexes. Ten animals of each sex had histopathological exams (including the nasal turbinates); the remaining two females were submitted to viral serology.

Effects noted in study and corresponding doses:

No treatment related mortality was observed; however, two control mice were found dead in cages and two high dose mice (one of each sex) were killed in *extremis* on days 5 and 6. A statistically significant decrease in weight (about 10% as compared to controls) was observed in both sexes at 80.0 ppm, and 89% of the males and 78% of the females showed minimal to mild inflammation of the nasal mucosa in the anterior segments of the nose. No such effects were observed at the lower doses or in controls.

Dose and endpoint used for MRL derivation:

[x] NOAEL [ ] LOAEL

30.5 ppm for no respiratory effects; LOAEL of 80 ppm for inflammation of the nasal mucosa in the anterior segments of the nose.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[xl 3 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain

None

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

NOAEL(ADJ) =30.5 ppm x 6 hr/24 hr x 5 d/7 d = 5.4 ppm

The $NOAEL_{[HEC]}$ is then calculated for a "gas:respiratory" effect in the extra thoracic region (EPA 1994) as follows:

The regional gas dose ratio for the extra thoracic region:
RGDR (ET) = $(V_E/SA)a/ (V_E/SA)h$ where V_E = the minute volume, and SA = the surface area of the extra thoracic region for the rat (a) and human (h), respectively.

$V_Ea = 0.046\ m^3/day$; $V_Eh = 20\ m^3/day$; $SA(ET)a = 3\ cm^2$; $SA(ET)h = 200\ cm^2$

RGDR (ET) = (0.046/3) / (20/200) = 0.15

$NOAEL_{[HEC]}$ = NOAEL (ADJ) x RGDR = 5.4 ppm x 0.15 = 0.81ppm

MRL = $NOAEL_{[HEC]}$ / UF = 0.81 ppm / 30 = 0.03 ppm

Other additional studies or pertinent information which lend support to this MRL:

In companion studies, 90-day vapor inhalation exposures were completed using Sprague-Dawley and Fischer-344 rats (CIIT 1983b, 1983c). Groups of 15 rats/sex/strain were exposed to hydrogen sulfide at 0, 10.1, 30.5 or 80 ppm 6 hours/day, 5 days/week. A significant reduction in body weight was noted at 80 ppm in female Sprague-Dawley rats (CIIT 1983c). Brain weight was reduced significantly (5%) in male Sprague-Dawley rats in the high-dose group and slightly, but not significantly, in females (CIIT 1983c). Histopathological examinations, including four sections of the nasal turbinates did not reveal any exposure-related effects in either strain of rats.

Severe alterations in the architecture and growth characteristics of Purkinje cell dendritic fields were noted in the offspring of Sprague-Dawley dams that had been exposed *in utero* to 20 ppm hydrogen sulfide for 7 hours/day from gestational days 5 through postpartum day 21 (Hannah and Roth 1991). As this was the lowest dose tested, there was no NOAEL for this effect. Similarly timed exposures, also in Sprague-Dawley dams, to 20 ppm hydrogen sulfide caused decreases in norepinephrine and increases in serotonin in the frontal cortex of the offspring (Skrajny et al. 1992). No NOAEL was identified because this was the lowest dose tested.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1,2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data

exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Kev to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Freauency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1 ,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for

the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) Q& A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-I

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/ m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a

NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEJ Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*)

(19) Kev to LSE Figure The Key explains the abbreviations and symbols used in the figure.

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

SAMPLE

1 →

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

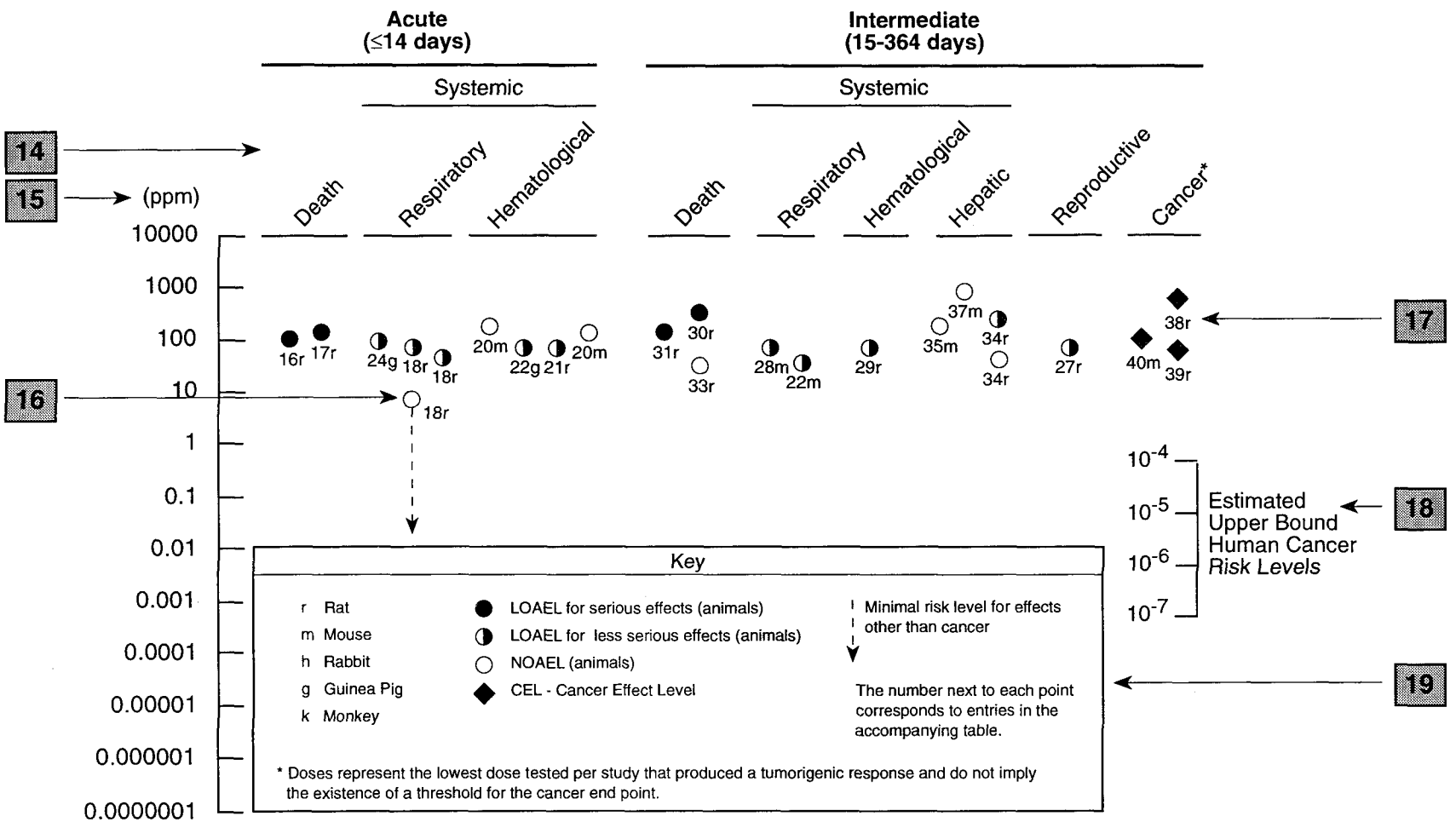
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE						
	5	6	7	8	9	10
3 → Systemic	↓	↓	↓	↓	↓	↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE						
					11	
Cancer					↓	
38	Rat	18 mo 5d/wk 7hr/d			20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information,

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
CI	confidence interval
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health

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IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration

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PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SIR	Standardized incidence ratio
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TRS	total reduced sulfur
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μmol	micromole
μg	microgram

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